SUBCHAPTER F—BIOLOGICS

PART 600—BIOLOGICAL PRODUCTS: GENERAL

Subpart A—General Provisions

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CROSS REFERENCES: For U.S. Customs Service regulations relating to viruses, serums, and toxins, see 19 CFR 12.21–12.23. For U.S. Postal Service regulations relating to the admissibility to the United States mails see parts 124 and 125 of the Domestic Mail Manual, that is incorporated by reference in 39 CFR part 111.

Subpart A—General Provisions

§ 600.3 Definitions.

As used in this subchapter:

(a) *Act* means the Public Health Service Act (58 Stat. 682), approved July 1, 1944.

(b) *Secretary* means the Secretary of Health and Human Services and any other officer or employee of the Department of Health and Human Services to whom the authority involved has been delegated.

(c) *Commissioner of Food and Drugs* means the Commissioner of the Food and Drug Administration.

(d) *Center for Biologics Evaluation and Research* means Center for Biologics Evaluation and Research of the Food and Drug Administration.

(e) *State* means a State or the District of Columbia, Puerto Rico, or the Virgin Islands.

(f) *Possession* includes among other possessions, Puerto Rico and the Virgin Islands.

(g) *Products* includes biological products and trivalent organic arsenicals.

(h) *Biological product* means any virus, therapeutic serum, toxin, antitoxin, or analogous product applicable to the prevention, treatment or cure of diseases or injuries of man:

(1) A virus is interpreted to be a product containing the minute living cause of an infectious disease and includes but is not limited to filterable viruses, bacteria, rickettsia, fungi, and protozoa.

(2) A therapeutic serum is a product obtained from blood by removing the clot or clot components and the blood cells.

(3) A toxin is a product containing a soluble substance poisonous to laboratory animals or to man in doses of 1 milliliter or less (or equivalent in weight) of the product, and having the property, following the injection of non-fatal doses into an animal, of causing to be produced therein another soluble substance which specifically neutralizes the poisonous substance and which is demonstrable in the serum of the animal thus immunized.

(4) An antitoxin is a product containing the soluble substance in serum or other body fluid of an immunized animal which specifically neutralizes the toxin against which the animal is immune.

(5) A product is analogous:

(i) To a virus if prepared from or with a virus or agent actually or potentially infectious, without regard to the degree of virulence or toxicogenicity of the specific strain used.

(ii) To a therapeutic serum, if composed of whole blood or plasma or containing some organic constituent or product other than a hormone or an

amino acid, derived from whole blood, plasma, or serum.

(iii) To a toxin or antitoxin, if intended, irrespective of its source of origin, to be applicable to the prevention, treatment, or cure of disease or injuries of man through a specific immune process.

(i) *Trivalent organic arsenicals* means arsphenamine and its derivatives (or any other trivalent organic arsenic compound) applicable to the prevention, treatment, or cure of diseases or injuries of man.

(j) A product is deemed *applicable to the prevention, treatment, or cure of diseases or injuries of man* irrespective of the mode of administration or application recommended, including use when intended through administration or application to a person as an aid in diagnosis, or in evaluating the degree of susceptibility or immunity possessed by a person, and including also any other use for purposes of diagnosis if the diagnostic substance so used is prepared from or with the aid of a biological product.

(k) *Proper name*, as applied to a product, means the name designated in the license for use upon each package of the product.

(l) *Dating period* means the period beyond which the product cannot be expected beyond reasonable doubt to yield its specific results.

(m) *Expiration date* means the calendar month and year, and where applicable, the day and hour, that the dating period ends.

(n) The word *standards* means specifications and procedures applicable to an establishment or to the manufacture or release of products, which are prescribed in this subchapter and which are designed to insure the continued safety, purity and potency of such products.

(o) The word *continued* as applied to the safety, purity and potency of products is interpreted to apply to the dating period.

(p) The word *safety* means the relative freedom from harmful effect to persons affected, directly or indirectly, by a product when prudently administered, taking into consideration the character of the product in relation to the condition of the recipient at the time.

(q) The word *sterility* is interpreted to mean freedom from viable contaminating microorganisms, as determined by the tests prescribed in §610.12 of this chapter.

(r) *Purity* means relative freedom from extraneous matter in the finished product, whether or not harmful to the recipient or deleterious to the product. *Purity* includes but is not limited to relative freedom from residual moisture or other volatile substances and pyrogenic substances.

(s) The word *potency* is interpreted to mean the specific ability or capacity of the product, as indicated by appropriate laboratory tests or by adequately controlled clinical data obtained through the administration of the product in the manner intended, to effect a given result.

(t) *Manufacturer* means any legal person or entity engaged in the manufacture of a product subject to license under the act; ''Manufacturer'' also includes any legal person or entity who is an applicant for a license where the applicant assumes responsibility for compliance with the applicable product and establishment standards.

(u) *Manufacture* means all steps in propagation or manufacture and preparation of products and includes but is not limited to filling, testing, labeling, packaging, and storage by the manufacturer.

(v) *Location* includes all buildings, appurtenances, equipment and animals used, and personnel engaged by a manufacturer within a particular area designated by an address adequate for identification.

(w) *Establishment* includes all locations.

(x) *Lot* means that quantity of uniform material identified by the manufacturer as having been thoroughly mixed in a single vessel.

(y) A *filling* refers to a group of final containers identical in all respects, which have been filled with the same product from the same bulk lot without any change that will affect the integrity of the filling assembly.

(z) *Process* refers to a manufacturing step that is performed on the product

itself which may affect its safety, purity or potency, in contrast to such manufacturing steps which do not affect intrinsically the safety, purity or potency of the product.

(aa) *Selling agent* or *distributor* means any person engaged in the unrestricted distribution, other than by sale at retail, of products subject to license.

(bb) *Container* (referred to also as ''final container'') is the immediate unit, bottle, vial, ampule, tube, or other receptacle containing the product as distributed for sale, barter, or exchange.

(cc) *Package* means the immediate carton, receptacle, or wrapper, including all labeling matter therein and thereon, and the contents of the one or more enclosed containers. If no package, as defined in the preceding sentence, is used, the container shall be deemed to be the package.

(dd) *Label* means any written, printed, or graphic matter on the container or package or any such matter clearly visible through the immediate carton, receptacle, or wrapper.

(ee) *Radioactive biological product* means a biological product which is labeled with a radionuclide or intended solely to be labeled with a radionuclide.

(ff) *Amendment* is the submission of information to a pending license application or supplement, to revise or modify the application as originally submitted.

(gg) *Supplement* is a request to the Director, Center for Biologics Evaluation and Research, to approve a change in an approved license application.

[38 FR 32048, Nov. 20, 1973, as amended at 40 FR 31313, July 25, 1975; 55 FR 11014, Mar. 26, 1990; 61 FR 24232, May 14, 1996; 62 FR 39901, July 24, 1997]

Subpart B—Establishment Standards

§ 600.10 Personnel.

(a) [Reserved]

(b) *Personnel.* Personnel shall have capabilities commensurate with their assigned functions, a thorough understanding of the manufacturing operations which they perform, the necessary training and experience relating to individual products, and adequate information concerning the application of the pertinent provisions of this subchapter to their respective functions. Personnel shall include such professionally trained persons as are necessary to insure the competent performance of all manufacturing processes.

(c) *Restrictions on personnel*—(1) *Specific duties.* Persons whose presence can affect adversely the safety and purity of a product shall be excluded from the room where the manufacture of a product is in progress.

(2) *Sterile operations.* Personnel performing sterile operations shall wear clean or sterilized protective clothing and devices to the extent necessary to protect the product from contamination.

(3) *Pathogenic viruses and spore-bearing organisms.* Persons working with viruses pathogenic for man or with spore-bearing microorganisms, and persons engaged in the care of animals or animal quarters, shall be excluded from areas where other products are manufactured, or such persons shall change outer clothing, including shoes, or wear protective covering prior to entering such areas.

(4) *Live vaccine work areas.* Persons may not enter a live vaccine processing area after having worked with other infectious agents in any other laboratory during the same working day. Only persons actually concerned with propagation of the culture, production of the vaccine, and unit maintenance, shall be allowed in live vaccine processing areas when active work is in progress. Casual visitors shall be excluded from such units at all times and all others having business in such areas shall be admitted only under supervision. Street clothing, including shoes, shall be replaced or covered by suitable laboratory clothing before entering a live vaccine processing unit. Persons caring for animals used in the manufacture of live vaccines shall be excluded from other animal quarters and from contact with other animals during the same working day.

[38 FR 32048, Nov. 20, 1973, as amended at 49 FR 23833, June 8, 1984; 55 FR 11014, Mar. 26, 1990; 62 FR 53538, Oct. 15, 1997]

§ 600.11 Physical establishment, equipment, animals, and care.

(a) *Work areas.* All rooms and work areas where products are manufactured or stored shall be kept orderly, clean, and free of dirt, dust, vermin and objects not required for manufacturing. Precautions shall be taken to avoid clogging and back-siphonage of drainage systems. Precautions shall be taken to exclude extraneous infectious agents from manufacturing areas. Work rooms shall be well lighted and ventilated. The ventilation system shall be arranged so as to prevent the dissemination of microorganisms from one manufacturing area to another and to avoid other conditions unfavorable to the safety of the product. Filling rooms, and other rooms where open, sterile operations are conducted, shall be adequate to meet manufacturing needs and such rooms shall be constructed and equipped to permit thorough cleaning and to keep air-borne contaminants at a minimum. If such rooms are used for other purposes, they shall be cleaned and prepared prior to use for sterile operations. Refrigerators, incubators and warm rooms shall be maintained at temperatures within applicable ranges and shall be free of extraneous material which might affect the safety of the product.

(b) *Equipment.* Apparatus for sterilizing equipment and the method of operation shall be such as to insure the destruction of contaminating microorganisms. The effectiveness of the sterilization procedure shall be no less than that achieved by an attained temperature of 121.5° C maintained for 20 minutes by saturated steam or by an attained temperature of 170° C maintained for 2 hours with dry heat. Processing and storage containers, filters, filling apparatus, and other pieces of apparatus and accessory equipment, including pipes and tubing, shall be designed and constructed to permit thorough cleaning and, where possible, inspection for cleanliness. All surfaces that come in contact with products shall be clean and free of surface solids, leachable contaminants, and other materials that will hasten the deterioration of the product or otherwise render it less suitable for the intended use. For products for which sterility is a factor, equipment shall be sterile, unless sterility of the product is assured by subsequent procedures.

(c) *Laboratory and bleeding rooms.* Rooms used for the processing of products, including bleeding rooms, shall be effectively fly-proofed and kept free of flies and vermin. Such rooms shall be so constructed as to insure freedom from dust, smoke and other deleterious substances and to permit thorough cleaning and disinfection. Rooms for animal injection and bleeding, and rooms for smallpox vaccine animals, shall be disinfected and be provided with the necessary water, electrical and other services.

(d) *Animal quarters and stables.* Animal quarters, stables and food storage areas shall be of appropriate construction, fly-proofed, adequately lighted and ventilated, and maintained in a clean, vermin-free and sanitary condition. No manure or refuse shall be stored as to permit the breeding of flies on the premises, nor shall the establishment be located in close proximity to off-property manure or refuse storage capable of engendering fly breeding.

(e) *Restrictions on building and equipment use*—(1) *Work of a diagnostic nature.* Laboratory procedures of a clinical diagnostic nature involving materials that may be contaminated, shall not be performed in space used for the manufacture of products except that manufacturing space which is used only occasionally may be used for diagnostic work provided spore-bearing pathogenic microorganisms are not involved and provided the space is thoroughly cleaned and disinfected before the manufacture of products is resumed.

(2) *Spore-bearing organisms for supplemental sterilization procedure control test.* Spore-bearing organisms used as an additional control in sterilization procedures may be introduced into areas used for the manufacture of products, only for the purposes of the test and only immediately before use for such purposes: *Provided,* That (i) the organism is not pathogenic for man or animals and does not produce pyrogens or toxins, (ii) the culture is demonstrated to be pure, (iii) transfer of test cultures to culture media shall be limited to the

sterility test area or areas designated for work with spore-bearing organisms, (iv) each culture be labeled with the name of the microorganism and the statement ''Caution: microbial spores. See directions for storage, use and disposition.'', and (v) the container of each culture is designed to withstand handling without breaking.

(3) *Work with spore-bearing organisms.* Except as provided in the previous paragraph, all work with spore-bearing microorganisms shall be done in an entirely separate building: *Provided,* That such work may be done in a portion of a building used in the manufacture of products not containing spore-bearing microorganisms if such portion is completely walled-off and is constructed so as to prevent contamination of other areas and if entrances to such portion are independent of the remainder of the building. All vessels, apparatus and equipment used for spore-bearing microorganisms shall be permanently identified and reserved exclusively for use with those organisms. Materials destined for further manufacturing may be removed from such an area only under conditions which will prevent the introduction of spores into other manufacturing areas.

(4) *Live vaccine processing.* Space used for processing a live vaccine shall not be used for any other purpose during the processing period for that vaccine and such space shall be decontaminated prior to initiation of the processing. Live vaccine processing areas shall be isolated from and independent of any space used for any other purpose by being either in a separate building, in a separate wing of a building, or in quarters at the blind end of a corridor and shall include adequate space and equipment for all processing steps up to filling into final containers. Test procedures which potentially involve the presence of microorganisms other than the vaccine strains, or the use of tissue culture cell lines other than primary cultures, shall not be conducted in space used for processing live vaccine.

(5) *Equipment and supplies—contamination.* Equipment and supplies used in work on or otherwise exposed to any pathogenic or potentially pathogenic agent shall be kept separated from equipment and supplies used in the manufacture of products to the extent necessary to prevent cross-contamination.

(f) *Animals used in manufacture*—(1) *Care of animals used in manufacturing.* Caretakers and attendants for animals used for the manufacture of products shall be sufficient in number and have adequate experience to insure adequate care. Animal quarters and cages shall be kept in sanitary condition. Animals on production shall be inspected daily to observe response to production procedures. Animals that become ill for reasons not related to production shall be isolated from other animals and shall not be used for production until recovery is complete. Competent veterinary care shall be provided as needed.

(2) *Quarantine of animals*—(i) *General.* No animal shall be used in processing unless kept under competent daily inspection and preliminary quarantine for a period of at least 7 days before use, or as otherwise provided in this subchapter. Only healthy animals free from detectable communicable diseases shall be used. Animals must remain in overt good health throughout the quarantine periods and particular care shall be taken during the quarantine periods to reject animals of the equine genus which may be infected with glanders and animals which may be infected with tuberculosis.

(ii) *Quarantine of monkeys.* In addition to observing the pertinent general quarantine requirements, monkeys used as a source of tissue in the manufacture of vaccine shall be maintained in quarantine for at least 6 weeks prior to use, except when otherwise provided in this part. Only monkeys that have reacted negatively to tuberculin at the start of the quarantine period and again within 2 weeks prior to use shall be used in the manufacture of vaccine. Due precaution shall be taken to prevent cross-infection from any infected or potentially infected monkeys on the premises. Monkeys to be used in the manufacture of a live vaccine shall be maintained throughout the quarantine period in cages closed on all sides with solid materials except the front which shall be screened, with no more than

two monkeys housed in one cage. Cage mates shall not be interchanged.

(3) *Immunization against tetanus.* Horses and other animals susceptible to tetanus, that are used in the processing steps of the manufacture of biological products, shall be treated adequately to maintain immunity to tetanus.

(4) *Immunization and bleeding of animals used as a source of products.* Toxins or other nonviable antigens administered in the immunization of animals used in the manufacture of products shall be sterile. Viable antigens, when so used, shall be free of contaminants, as determined by appropriate tests prior to use. Injections shall not be made into horses within 6 inches of bleeding site. Horses shall not be bled for manufacturing purposes while showing persistent general reaction or local reaction near the site of bleeding. Blood shall not be used if it was drawn within 5 days of injecting the animals with viable microorganisms. Animals shall not be bled for manufacturing purposes when they have an intercurrent disease. Blood intended for use as a source of a biological product shall be collected in clean, sterile vessels. When the product is intended for use by injection, such vessels shall also be pyrogen-free.

(5) [Reserved]

(6) *Reporting of certain diseases.* In cases of actual or suspected infection with foot and mouth disease, glanders, tetanus, anthrax, gas gangrene, equine infectious anemia; equine encephalomyelitis, or any of the pock diseases among animals intended for use or used in the manufacture of products, the manufacturer shall immediately notify the Director, Center for Biologics Evaluation and Research.

(7) *Monkeys used previously for experimental or test purposes.* Monkeys that have been used previously for experimental or test purposes with live microbiological agents shall not be used as a source of kidney tissue for the manufacture of vaccine. Except as provided otherwise in this subchapter, monkeys that have been used previously for other experimental or test purposes may be used as a source of kidney tissue upon their return to a normal condition, provided all quarantine requirements have been met.

(8) *Necropsy examination of monkeys.* Each monkey used in the manufacture of vaccine shall be examined at necropsy under the direction of a qualified pathologist, physician, or veterinarian having experience with diseases of monkeys, for evidence of ill health, particularly for (i) evidence of tuberculosis, (ii) presence of herpes-like lesions, including eruptions or plaques on or around the lips, in the buccal cavity or on the gums, and (iii) signs of conjunctivitis. If there are any such signs or other significant gross pathological lesions, the tissue shall not be used in the manufacture of vaccine.

(g) *Filling procedures.* Filling procedures shall be such as will not affect adversely the safety, purity or potency of the product.

(h) *Containers and closures.* All final containers and closures shall be made of material that will not hasten the deterioration of the product or otherwise render it less suitable for the intended use. All final containers and closures shall be clean and free of surface solids, leachable contaminants and other materials that will hasten the deterioration of the product or otherwise render it less suitable for the intended use. After filling, sealing shall be performed in a manner that will maintain the integrity of the product during the dating period. In addition, final containers and closures for products intended for use by injection shall be sterile and free from pyrogens. Except as otherwise provided in the regulations of this subchapter, final containers for products intended for use by injection shall be colorless and sufficiently transparent to permit visual examination of the contents under normal light. As soon as possible after filling final containers shall be labeled as prescribed in § 610.60 *et seq.* of this chapter, except that final containers may be stored without such prescribed labeling provided they are stored in a sealed receptacle labeled both inside and outside with at least the name of the product, the lot number, and the filling identification.

[38 FR 32048, Nov. 20, 1973, as amended at 41 FR 10428, Mar. 11, 1976; 49 FR 23833, June 8, 1984; 55 FR 11013, Mar. 26, 1990]

§ 600.12 Records.

(a) *Maintenance of records.* Records shall be made, concurrently with the performance, of each step in the manufacture and distribution of products, in such a manner that at any time successive steps in the manufacture and distribution of any lot may be traced by an inspector. Such records shall be legible and indelible, shall identify the person immediately responsible, shall include dates of the various steps, and be as detailed as necessary for clear understanding of each step by one experienced in the manufacture of products.

(b) *Records retention*—(1) *General.* Records shall be retained for such interval beyond the expiration date as is necessary for the individual product, to permit the return of any clinical report of unfavorable reactions. The retention period shall be no less than five years after the records of manufacture have been completed or six months after the latest expiration date for the individual product, whichever represents a later date.

(2) *Records of recall.* Complete records shall be maintained pertaining to the recall from distribution of any product upon notification by the Director, Center for Biologics Evaluation and Research, to recall for failure to conform with the standards prescribed in the regulations of this subchapter, because of deterioration of the product or for any other factor by reason of which the distribution of the product would constitute a danger to health.

(3) *Suspension of requirement for retention.* The Director, Center for Biologics Evaluation and Research, may authorize the suspension of the requirement to retain records of a specific manufacturing step upon a showing that such records no longer have significance for the purposes for which they were made: *Provided,* That a summary of such records shall be retained.

(c) *Records of sterilization of equipment and supplies.* Records relating to the mode of sterilization, date, duration, temperature and other conditions relating to each sterilization of equipment and supplies used in the processing of products shall be made by means of automatic recording devices or by means of a system of recording which gives equivalent assurance of the accuracy and reliability of the record. Such records shall be maintained in a manner that permits an identification of the product with the particular manufacturing process to which the sterilization relates.

(d) *Animal necropsy records.* A necropsy record shall be kept on each animal from which a biological product has been obtained and which dies or is sacrificed while being so used.

(e) *Records in case of divided manufacturing responsibility.* If two or more establishments participate in the manufacture of a product, the records of each such establishment must show plainly the degree of its responsibility. In addition, each participating manufacturer shall furnish to the manufacturer who prepares the product in final form for sale, barter or exchange, a copy of all records relating to the manufacturing operations performed by such participating manufacturer insofar as they concern the safety, purity and potency of the lots of the product involved, and the manufacturer who prepares the product in final form shall retain a complete record of all the manufacturing operations relating to the product.

[38 FR 32048, Nov. 20, 1973, as amended at 49 FR 23833, June 8, 1984; 55 FR 11013, Mar. 26, 1990]

§ 600.13 Retention samples.

Manufacturers shall retain for a period of at least 6 months after the expiration date, unless a different time period is specified in additional standards, a quantity of representative material of each lot of each product, sufficient for examination and testing for safety and potency, except Whole Blood, Cryoprecipitated AHF, Platelets, Red Blood Cells, Plasma, and Source Plasma and Allergenic Products prepared to a physician's prescription. Samples so retained shall be selected at random from either final container material, or from bulk and final containers, provided they include at least one final container as a final package, or package-equivalent of such filling of each lot of the product as intended for distribution. Such sample material shall be stored at temperatures and under conditions which will maintain

the identity and integrity of the product. Samples retained as required in this section shall be in addition to samples of specific products required to be submitted to the Center for Biologics Evaluation and Research. Exceptions may be authorized by the Director, Center for Biologics Evaluation and Research, when the lot yields relatively few final containers and when such lots are prepared by the same method in large number and in close succession.

[41 FR 10428, Mar. 11, 1976, as amended at 49 FR 23833, June 8, 1984; 50 FR 4133, Jan. 29, 1985; 55 FR 11013, Mar. 26, 1990]

§ 600.14 Reporting of errors.

(a) The Director, Office of Compliance, Center for Biologics Evaluation and Research (HFB–100), 8800 Rockville Pike, Bethesda, MD 20892, shall be notified promptly of errors or accidents in the manufacture of products that may affect the safety, purity, or potency of any product.

(b) Manufacturers of licensed in vitro diagnostic products, and manufacturers of unlicensed in vitro diagnostic products which are required to be registered under part 607 of this chapter, shall notify the Director in accordance with paragraph (a) of this section. Manufacturers of other in vitro diagnostic products which are required to be registered under part 807 of this chapter, shall report in accordance with part 803 of this chapter.

[38 FR 32048, Nov. 20, 1973, as amended at 49 FR 23833, June 8, 1984; 49 FR 36348, Sept. 14, 1984; 55 FR 11014, Mar. 26, 1990]

§ 600.15 Temperatures during shipment.

The following products shall be maintained during shipment at the specified temperatures:

(a) *Products.*

Product	Temperature
Cryoprecipitated AHF	−18 °C or colder.
Measles and Rubella Virus Vaccine Live.	10 °C or colder.
Measles Live and Smallpox Vaccine.	Do.
Measles, Mumps, and Rubella Virus Vaccine Live.	Do.
Measles and Mumps Virus Vaccine Live.	Do.
Measles Virus Vaccine Live	Do.
Mumps Virus Vaccine Live	Do.
Fresh Frozen Plasma	−18 °C or colder.
Liquid Plasma	1 to 10 °C.
Plasma	−18 °C or colder.
Platelet Rich Plasma	Between 1 and 10 °C if the label indicates storage between 1 and 6 °C, or all reasonable methods to maintain the temperature as close as possible to a range between 20 and 24 °C, if the label indicates storage between 20 and 24 °C.
Platelets	Between 1 and 10 °C if the label indicates storage between 1 and 6 °C, or all reasonable methods to maintain the temperature as close as possible to a range between 20 to 24 °C, if the label indicates storage between 20 and 24 °C.
Poliovirus Vaccine Live Oral Trivalent.	0 °C or colder.
Poliovirus Vaccine Live Oral Type I.	Do.
Poliovirus Vaccine Live Oral Type II.	Do.
Poliovirus Vaccine Live Oral Type III.	Do.
Red Blood Cells (liquid product).	Between 1 and 10 °C.
Red Blood Cells Frozen	−65 °C or colder.
Rubella and Mumps Virus Vaccine Live.	10 °C or colder.
Rubella Virus Vaccine Live	Do.
Smallpox Vaccine (Liquid Product).	0 °C or colder.
Source Plasma	−5 °C or colder.
Source Plasma Liquid	10 °C or colder.
Whole Blood	Blood that is transported from the collecting facility to the processing facility shall be transported in an environment capable of continuously cooling the blood toward a temperature range of 1 to 10 °C, or at a temperature as close as possible to 20 to 24 °C for a period not to exceed 6 hours. Blood transported from the storage facility shall be placed in an appropriate environment to maintain a temperature range between 1 to 10 °C during shipment.
Yellow Fever Vaccine	0 °C or colder.

(b) *Exemptions.* Exemptions or modifications shall be made only upon written approval, in the form of a supplement of the product license, issued by the Director, Center for Biologics Evaluation and Research.

[39 FR 39872, Nov. 12, 1974, as amended at 49 FR 23833, June 8, 1984; 50 FR 4133, Jan. 29, 1985; 50 FR 9000, Mar. 6, 1985; 55 FR 11013, Mar. 26, 1990; 59 FR 49351, Sept. 28, 1994]

Subpart C—Establishment Inspection

§ 600.20 Inspectors.

Inspections shall be made by an officer of the Food and Drug Administration having special knowledge of the methods used in the manufacture and control of products and designated for such purposes by the Commissioner of Food and Drugs, or by any officer, agent, or employee of the Department of Health and Human Services specifically designated for such purpose by the Secretary.

[38 FR 32048, Nov. 20, 1973]

§ 600.21 Time of inspection.

The inspection of an establishment for which a license is pending need not be made until the establishment is in operation and is manufacturing the complete product for which a product license is desired. In case the license is denied following inspection for the original license, no reinspection need be made until assurance has been received that the faulty conditions which were the basis of the denial have been corrected. An inspection of each licensed establishment and its additional location(s) shall be made at least once every 2 years. Inspections may be made with or without notice, and shall be made during regular business hours unless otherwise directed.

[38 FR 32048, Nov. 20, 1973, as amended at 48 FR 26314, June 7, 1983]

§ 600.22 Duties of inspector.

The inspector shall:

(a) Call upon the active head of the establishment, stating the object of his visit,

(b) Interrogate the proprietor or other personnel of the establishment as he may deem necessary,

(c) Examine the details of location, construction, equipment and maintenance, including stables, barns, warehouses, manufacturing laboratories, bleeding clinics maintained for the collection of human blood, shipping rooms, record rooms, and any other structure or appliance used in any part of the manufacture of a product,

(d) Investigate as fully as he deems necessary the methods of propagation, processing, testing, storing, dispensing, recording, or other details of manufacture and distribution of each licensed product, or product for which a license has been requested, including observation of these procedures in actual operation,

(e) Obtain and cause to be sent to the Director, Center for Biologics Evaluation and Research, adequate samples for the examination of any product or ingredient used in its manufacture,

(f) Bring to the attention of the manufacturer any fault observed in the course of inspection in location, construction, manufacturing methods, or administration of a licensed establishment which might lead to impairment of a product,

(g) Inspect and copy, as circumstances may require, any records required to be kept pursuant to § 600.12,

(h) Certify as to the condition of the establishment and of the manufacturing methods followed and make recommendations as to action deemed appropriate with respect to any application for license or any license previously issued.

[38 FR 32048, Nov. 20, 1973, as amended at 49 FR 23833, June 8, 1984; 55 FR 11013, Mar. 26, 1990]

Subpart D—Reporting of Adverse Experiences

SOURCE: 59 FR 54042, Oct. 27, 1994, unless otherwise noted.

§ 600.80 Postmarketing reporting of adverse experiences.

(a) *Definitions.* The following definitions of terms apply to this section:

Adverse experience. Any adverse event associated with the use of a biological product in humans, whether or not considered product related, including the following: An adverse event occurring in the course of the use of a biological product in professional practice; an adverse event occurring from overdose of the product whether accidental or intentional; an adverse event occurring from abuse of the product; an adverse event occurring from withdrawal of the product; and any failure of expected pharmacological action.

Blood Component. As defined in § 606.3(c) of this chapter.

Disability. A substantial disruption of a person's ability to conduct normal life functions.

Life-threatening adverse experience. Any adverse experience that places the patient, in the view of the initial reporter, at immediate risk of death from the adverse experience as it occurred, i.e., it does not include an adverse experience that, had it occurred in a more severe form, might have caused death.

Serious adverse experience. Any adverse experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Unexpected adverse experience: Any adverse experience that is not listed in the current labeling for the biological product. This includes events that may be symptomatically and pathophysiologically related to an event listed in the labeling, but differ from the event because of greater severity or specificity. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the labeling only referred to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the labeling only listed cerebral vascular accidents. ''Unexpected,'' as used in this definition, refers to an adverse experience that has not been previously observed (i.e., included in the labeling) rather than from the perspective of such experience not being anticipated from the pharmacological properties of the pharmaceutical product.

(b) *Review of adverse experiences.* Any person having a product license under § 601.20 of this chapter shall promptly review all adverse experience information pertaining to its product obtained or otherwise received by the licensed manufacturer from any source, foreign or domestic, including information derived from commercial marketing experience, postmarketing clinical investigations, postmarketing epidemiological/surveillance studies, reports in the scientific literature, and unpublished scientific papers. Licensed manufacturers are not required to resubmit to FDA adverse product experience reports forwarded to the licensed manufacturer by FDA; licensed manufacturers, however, must submit all followup information on such reports to FDA. Any person subject to the reporting requirements under paragraph (c) of this section shall also develop written procedures for the surveillance, receipt, evaluation, and reporting of postmarketing adverse experiences to FDA.

(c) *Reporting requirements.* The licensed manufacturer shall report to FDA adverse experience information, as described in this section. The licensed manufacturer shall submit two copies of each report described in this section for nonvaccine biological products, to the Center for Biologics Evaluation and Research (HFM–210), Food and Drug Administration, 1401 Rockville Pike, suite 200 N., Rockville, MD 20852–1448. Submit all vaccine adverse experience reports to: Vaccine Adverse Event Reporting System (VAERS), P.O. Box 1100, Rockville, MD 20849–1100. FDA may waive the requirement for the second copy in appropriate instances.

(1)(i) *Postmarketing 15-day ''Alert reports''.* The licensed manufacturer shall report each adverse experience that is both serious and unexpected, whether foreign or domestic, as soon as possible but in no case later than 15 calendar days of initial receipt of the information by the licensed manufacturer.

(ii) *Postmarketing 15-day ''Alert reports''—followup.* The licensed manufacturer shall promptly investigate all adverse experiences that are the subject of these postmarketing 15-day Alert reports and shall submit followup reports within 15 calendar days of receipt of new information or as requested by FDA. If additional information is not obtainable, records should be maintained of the unsuccessful steps taken to seek additional information. Postmarketing 15-day Alert reports and followups to them shall be submitted under separate cover.

(iii) *Submission of reports.* The requirements of paragraphs (c)(1)(i) and (c)(1)(ii) of this section, concerning the submission of postmarketing 15-day Alert reports, shall also apply to any person whose name appears on the label of a licensed biological product as a manufacturer, packer, distributor, shared manufacturer, joint manufacturer, or any other participant involved in divided manufacturing. To avoid unnecessary duplication in the submission to FDA of reports required by paragraphs (c)(1)(i) and (c)(1)(ii) of this section, obligations of persons other than the licensed manufacturer of the final biological product may be met by submission of all reports of serious adverse experiences to the licensed manufacturer of the final product. If a person elects to submit adverse experience reports to the licensed manufacturer of the final product rather than to FDA, the person shall submit each report to the licensed manufacturer of the final product within 5 calendar days of receipt of the report by the person, and the licensed manufacturer of the final product shall then comply with the requirements of this section. Under this circumstance, a person who elects to submit reports to the licensed manufacturer of the final product shall maintain a record of this action which shall include:

(A) A copy of all adverse biological product experience reports submitted to the licensed manufacturer of the final product;

(B) The date the report was received by the person;

(C) The date the report was submitted to the licensed manufacturer of the final product; and–

(D) The name and address of the licensed manufacturer of the final product.

(iv) *Report identification.* Each report submitted under this paragraph shall bear prominent identification as to its contents, i.e., ''15-day Alert report,'' or ''15-day Alert report-followup.''

(2) *Periodic adverse experience reports.* (i) The licensed manufacturer shall report each adverse experience not reported under paragraph (c)(1)(i) of this section at quarterly intervals, for 3 years from the date of issuance of the product license, and then at annual intervals. The licensed manufacturer shall submit each quarterly report within 30 days of the close of the quarter (the first quarter beginning on the date of issuance of the product license) and each annual report within 60 days of the anniversary date of the issuance of the product license. Upon written notice, FDA may extend or reestablish the requirement that a licensed manufacturer submit quarterly reports, or require that the licensed manufacturer submit reports under this section at different times than those stated. Followup information to adverse experiences submitted in a periodic report may be submitted in the next periodic report.

(ii) Each periodic report shall contain:

(A) A narrative summary and analysis of the information in the report and an analysis of the 15-day Alert reports submitted during the reporting interval (all 15-day Alert reports being appropriately referenced by the licensed manufacturer's patient identification number, adverse reaction term(s), and date of submission to FDA);

(B) A form designated for Adverse Experience Reporting by FDA for each adverse experience not reported under paragraph (c)(1)(i) of this section (with an index consisting of a line listing of the licensed manufacturer's patient identification number and adverse reaction term(s)); and

(C) A history of actions taken since the last report because of adverse experiences (for example, labeling changes or studies initiated).

(iii) Periodic reporting, except for information regarding 15-day Alert reports, does not apply to adverse experience information obtained from postmarketing studies (whether or not conducted under an investigational new drug application), from reports in the scientific literature, and from foreign marketing experience.

(d) *Scientific literature.* (1) A 15-day Alert report based on information from the scientific literature shall be accompanied by a copy of the published article. The 15-day Alert reporting requirements in paragraph (c)(1)(i) of this section (i.e., serious, unexpected adverse experiences) apply only to reports found in scientific and medical journals either as case reports or as the result of a formal clinical trial.

(2) As with all reports submitted under paragraph (c)(1)(i) of this section, reports based on the scientific literature shall be submitted on the reporting form designated by FDA or comparable format as prescribed by paragraph (f) of this section. In cases where the licensed manufacturer believes that preparing the form designated by FDA constitutes an undue hardship, the licensed manufacturer may arrange with the Division of Biostatistics and Epidemiology (HFM–210) for an acceptable alternative reporting format.

(e) *Postmarketing studies.* (1) Licensed manufacturers are not required to submit a 15-day Alert report under paragraph (c) of this section for an adverse experience obtained from a postmarketing clinical study (whether or not conducted under a biological investigational new drug application) unless the licensed manufacturer concludes that there is a reasonable possibility that the product caused the adverse experience.

(2) The licensed manufacturer shall separate and clearly mark reports of adverse experiences that occur during a postmarketing study as being distinct from those experiences that are being reported spontaneously to the licensed manufacturer.

(f) *Reporting forms.* (1) Except as provided in paragraph (f)(3) of this section, the licensed manufacturer shall complete the reporting form designated by FDA for each report of an adverse experience (FDA Form 3500A, or, for vaccines, a VAERS form; foreign events including those associated with the use of vaccines, may be submitted either on an FDA Form 3500A or, if preferred, on a CIOMS I form).

(2) Each completed form should refer only to an individual patient or single attached publication.

(3) Instead of using a designated reporting form, a licensed manufacturer may use a computer-generated form or other alternative format (e.g., a computer-generated tape or tabular listing) provided that:

(i) The content of the alternative format is equivalent in all elements of information to those specified in the form designated by FDA; and

(ii) the format is approved in advance by MEDWATCH: The FDA Medical Products Reporting Program; or, for alternatives to the VAERS Form, by the Division of Biostatistics and Epidemiology.

(4) Copies of the reporting form designated by FDA (FDA–3500A) for nonvaccine biological products may be obtained from the Center for Biologics Evaluation and Research (address above). Additional supplies of the form may be obtained from the Consolidated Forms and Publications Distribution Center, 3222 Hubbard Rd., Landover, MD 20785. Supplies of the VAERS form may be obtained from VAERS by calling 1–800–822–7967.

(g)*Multiple reports.* A licensed manufacturer should not include in reports under this section any adverse experience that occurred in clinical trials if they were previously submitted as part of the license application. If a report refers to more than one biological product marketed by a licensed manufacturer, the licensed manufacturer should submit the report to the license for the product listed first in the report.

(h) *Patient privacy.* For nonvaccine biological products, a licensed manufacturer should not include in reports under this section the names and addresses of individual patients; instead, the licensed manufacturer should assign a unique code number to each report, preferably not more than eight characters in length. The licensed manufacturer should include the name of

the reporter from whom the information was received. The names of patients, health care professionals, hospitals, and geographical identifiers in adverse experience reports are not releasable to the public under FDA's public information regulations in part 20 this of chapter. For vaccine adverse experience reports, these data will become part of the CDC Privacy Act System 09–20–0136, ''Epidemiologic Studies and Surveillance of Disease Problems.'' Information identifying the person who received the vaccine or that person's legal representative will not be made available to the public, but may be available to the vaccinee or legal representative.

(i) *Recordkeeping.* The licensed manufacturer shall maintain for a period of 10 years records of all adverse experiences known to the licensed manufacturer, including raw data and any correspondence relating to the adverse experiences.

(j) *Revocation of license.* If a licensed manufacturer fails to establish and maintain records and make reports required under this section with respect to a licensed biological product, FDA may revoke the product license for such a product in accordance with the procedures of §601.5 of this chapter.

(k) *Exemptions.* Manufacturers of the following listed products are not required to submit adverse experience reports under this section:

(1) Whole blood or components of whole blood.

(2) In vitro diagnostic products, including assay systems for the detection of antibodies or antigens to retroviruses. These products are subject to the reporting requirements for devices.

(l) *Disclaimer.* A report or information submitted by a licensed manufacturer under this section (and any release by FDA of that report or information) does not necessarily reflect a conclusion by the licensed manufacturer or FDA that the report or information constitutes an admission that the biological product caused or contributed to an adverse effect. A licensed manufacturer need not admit, and may deny, that the report or information submitted under this section constitutes an admission that the biological product caused or contributed to an adverse effect. For purposes of this provision, this paragraph also includes any person reporting under paragraph (c)(1)(iii) of this section.

[59 FR 54042, Oct. 27, 1994, as amended at 62 FR 34168, June 25, 1997; 62 FR 52252, Oct. 7, 1997; 63 FR 14612, Mar. 26, 1998]

EFFECTIVE DATE NOTE: At 62 FR 52252, Oct. 7, 1997, §600.80 was amended by revising paragraphs (a), (c)(1), (f)(1), and the first sentence of paragraph (g); by adding two new sentences at the end of paragraph (b); and by removing paragraph (j) and redesignating paragraphs (k), (l), and (m) as paragraphs (j), (k), and (l), respectively, effective Apr. 6, 1998. At 63 FR 14612, Mar. 26, 1998, the last sentence of paragraph (l) was corrected by revising ''(c)(1)(ii)'' to read ''(c)(1)(iii)'', effective April 6, 1998. For the convenience of the user, the superseded text follows:

§600.80 Postmarketing reporting of adverse experiences.

(a) *Definitions.* The following definitions of terms apply to this section:

Adverse experience means any adverse event associated with the use of a biological product in humans, whether or not considered product related, including the following: an adverse event occurring in the course of the use of a biological product in professional practice; an adverse event occurring from overdose of the product, whether accidental or intentional; an adverse event occurring from abuse of the product; an adverse event occurring from withdrawal of the product; and any failure of expected pharmacological action.

Blood Component for this purpose has the same meaning as defined in §606.3(c) of this chapter.

Serious means an adverse experience associated with the use of a biological product that is fatal or life-threatening, is permanently disabling, requires inpatient hospitalization, or is a congenital anomaly, cancer, or overdose.

Unexpected means an adverse biological product experience that is not listed in the current labeling for the product and includes an event that may be symptomatically and pathophysiologically related to an event listed in the labeling, but differs from the event because of greater severity or specificity. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the labeling only referred to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the labeling only listed cerebral vascular accidents.

* * * * *

(c)* * *

(1) *Fifteen-day Alert reports.* (i) The licensed manufacturer shall report each adverse experience that is both serious and unexpected, regardless of source, as soon as possible but in any case within 15 working days of initial receipt of the information. These reports are required to be submitted, for nonvaccine biological products, on a form designated by FDA or a suitable format containing all of the data elements in the FDA designated reporting form, and, for vaccines on a VAERS form. The licensed manufacturer shall promptly investigate all adverse experiences that are the subject of these 15-day Alert reports and shall submit followup reports within 15 working days of receipt of new information or as requested by FDA. If additional information is not obtainable, a followup report may be required that describes briefly the steps taken to seek additional information and the reasons why it could not be obtained. These 15-day Alert reports and followups to them are required to be submitted under separate cover and may not be included, except for summary or tabular purposes, in a periodic report.

(ii) The requirements of paragraph (c)(1)(i) of this section, concerning the submission of 15-day Alert reports, shall also apply to any person other than the licensed manufacturer of the final product whose name appears on the label of a licensed biological product as a manufacturer, packer, distributor, shared manufacturer, joint manufacturer, or any other participant involved in divided manufacturing. In order to avoid unnecessary duplication in the initial and followup submission of reports to FDA, the obligations of a manufacturer other than the licensed manufacturer, may be met by submitting all reports to the licensed manufacturer of the final product. If a manufacturer other than the licensed manufacturer elects to submit reports to the licensed manufacturer rather than to FDA, it shall submit each report to the licensed manufacturer within 3 working days of its receipt, and the licensed manufacturer shall then comply with the requirements of this section. Under this circumstance, the manufacturer shall maintain a record of this action which shall include:

(A) A copy of all adverse biological product experience reports submitted to the licensed manufacturer,

(B) Date the report was received by the manufacturer,

(C) Date the report was submitted to the licensed manufacturer,

(D) Name and address of the licensed manufacturer.

(iii) Each report submitted under this paragraph shall bear prominent identification as to its contents, i.e., ''15-day Alert report'' or ''15-day Alert report--followup.''

* * * * *

(f) *Reporting forms.* (1) Except as provided in paragraph (f)(3) of this section, the licensed manufacturer shall complete the reporting form designated by FDA (FDA–3500A, or, for vaccines, a VAERS form) for each report of an adverse experience.

* * * * *

(g) *Multiple reports.* A licensed manufacturer should not include in reports under this section any adverse experiences that occurred in clinical trials if they were previously submitted in the product license application.* * *

* * * * *

(j) *Guideline.* FDA has prepared a guideline for the submission of reports of adverse experiences and suggested followup investigation of reports.

§ 600.81 Distribution reports.

The licensed manufacturer shall submit information about the quantity of the product distributed under the product license, including the quantity distributed to distributors. The interval between distribution reports shall be 6 months. Upon written notice, FDA may require that the licensed manufacturer submit distribution reports under this section at times other than every 6 months. The distribution report shall consist of the bulk lot number (from which the final container was filled), the fill lot numbers for the total number of dosage units of each strength or potency distributed (e.g., fifty thousand per 10-milliliter vials), the label lot number (if different from fill lot number), labeled date of expiration, number of doses in fill lot/label lot, date of release of fill lot/label lot for distribution at that time. If any significant amount of a fill lot/label lot is returned, include this information. Disclosure of financial or pricing data is not required. As needed, FDA may require submission of more detailed product distribution information. Upon written notice, FDA may require that the licensed manufacturer submit reports under this section at times other than those stated. Requests by a licensed manufacturer to submit reports at times other than those stated should be made as a request for a waiver under § 600.90.

§ 600.90 Waivers.

(a) A licensed manufacturer may ask the Food and Drug Administration to waive under this section any requirement that applies to the licensed manufacturer under §§ 600.80 and 600.81. A waiver request under this section is required to be submitted with supporting documentation. The waiver request is required to contain one of the following:

(1) An explanation why the licensed manufacturer's compliance with the requirement is unnecessary or cannot be achieved,

(2) A description of an alternative submission that satisfies the purpose of the requirement, or

(3) Other information justifying a waiver.

(b) FDA may grant a waiver if it finds one of the following:

(1) The licensed manufacturer's compliance with the requirement is unnecessary or cannot be achieved,

(2) The licensed manufacturer's alternative submission satisfies the requirement, or

(3) The licensed manufacturer's submission otherwise justifies a waiver.

PART 601—LICENSING

Subpart A—General Provisions

Sec.

Subpart B—Establishment Licensing

Subpart C—Product Licensing

Subpart D—Licensing of Foreign Establishments and Products

Subpart E—Accelerated Approval of Biological Products for Serious or Life-Threatening Illnesses

Subpart F—Confidentiality of Information

AUTHORITY: 21 U.S.C. 321, 351, 352, 353, 355, 360, 360c–360f, 360h–360j, 371, 374, 379e, 381; 42 U.S.C. 216, 241, 262, 263; 15 U.S.C. 1451–1561.

SOURCE: 38 FR 32052, Nov. 20, 1973, unless otherwise noted.

CROSS REFERENCES: For U.S. Customs Service regulations relating to viruses, serums, and toxins, see 19 CFR 12.21–12.23. For U.S. Postal Service regulations relating to the admissibility to the United States mails see parts 124 and 125 of the Domestic Mail Manual, that is incorporated by reference in 39 CFR part 111.

Subpart A—General Provisions

§ 601.1 Two forms of licenses.

There shall be two forms of licenses: establishment and product.

§ 601.2 Applications for establishment and product licenses; procedures for filing.

(a) *General.* To obtain a license for any establishment or product, the manufacturer shall make application

to the Director, Center for Biologics Evaluation and Research, on forms prescribed for such purposes, and in the case of an application for a product license, shall submit data derived from nonclinical laboratory and clinical studies which demonstrate that the manufactured product meets prescribed standards of safety, purity, and potency; with respect to each nonclinical laboratory study, either a statement that the study was conducted in compliance with the requirements set forth in part 58 of this chapter, or, if the study was not conducted in compliance with such regulations, a brief statement of the reason for the noncompliance; statements regarding each clinical investigation involving human subjects contained in the application, that it either was conducted in compliance with the requirements for institutional review set forth in part 56 of this chapter or was not subject to such requirements in accordance with § 56.104 or § 56.105, and was conducted in compliance with requirements for informed consent set forth in part 50 of this chapter; a full description of manufacturing methods; data establishing stability of the product through the dating period; sample(s) representative of the product to be sold, bartered, or exchanged or offered, sent, carried or brought for sale, barter, or exchange; summaries of results of tests performed on the lot(s) represented by the submitted sample(s); and specimens of the labels, enclosures, and containers proposed to be used for the product. The applicant shall also include a financial certification or disclosure statement(s) or both for clinical investigators as required by part 54 of this chapter. An application for license shall not be considered as filed until all pertinent information and data have been received from the manufacturer by the Center for Biologics Evaluation and Research. The applicant shall also include either a claim for categorical exclusion under § 25.30 or 25.31 of this chapter or an environmental assessment under § 25.40 of this chapter. In lieu of the procedures described in this paragraph, applications for radioactive biological products shall be handled as set forth in paragraph (b) of this section. The applicant, or the applicant's attorney, agent, or other authorized official shall sign the application. In lieu of the procedures described in this paragraph, applications for the following specified categories of products shall be handled as set forth in paragraph (c) of this section:

(1) Therapeutic DNA plasmid products;

(2) Therapeutic synthetic peptide products of 40 or fewer amino acids;

(3) Monoclonal antibody products for in vivo use; and

(4) Therapeutic recombinant DNA-derived products.

(b) *Radioactive biological products.* In lieu of submitting an establishment and product license for the manufacture of a radioactive biological product, as defined in § 600.3(ee) of this chapter, the manufacturer of such a product shall submit a new drug application to the Director, Division of Medical Imaging, Surgical, and Dental Products (HFD–160), Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, consistent with the procedures set forth in § 314.50 of this chapter. For such products, the approval of the new drug application will be in lieu of issuing a product and an establishment license. Compliance with the provisions of part 314 of this chapter shall be deemed to constitute compliance with the provisions of Subchapter F of this chapter unless the Commissioner makes a determination that a particular regulation from Subchapter F shall be applicable to radioactive drugs containing a biological product, e.g., § 610.2 of this chapter.

(c)(1) To obtain marketing approval for a therapeutic DNA plasmid product, therapeutic synthetic peptide product of 40 or fewer amino acids, monoclonal antibody product for in vivo use, or therapeutic recombinant DNA-derived product, an applicant shall submit to the Director, Center for Biologics Evaluation and Research, a biologics license application on a form prescribed by the Director, Center for Biologics Evaluation and Research. For such products, a separate establishment license application shall not be required. An application for a license for such a product shall include:

(i) Data derived from nonclinical laboratory and clinical studies that demonstrate that the manufactured product meets prescribed standards of safety, purity, and potency; with respect to each nonclinical laboratory study, either a statement that the study was conducted in compliance with the requirements set forth in part 58 of this chapter, or,

(ii) If the study was not conducted in compliance with such regulations, a brief statement of the reason for the noncompliance;

(iii) Statements regarding each clinical investigation involving human subjects contained in the application, that it either was conducted in compliance with the requirements for institutional review set forth in part 56 of this chapter or was not subject to such requirements in accordance with §§56.104 or 56.105 of this chapter, and was conducted in compliance with requirements for informed consent set forth in part 50 of this chapter;

(iv) A full description of manufacturing methods;

(v) Data establishing stability of the product through the dating period;

(vi) Sample(s) representative of the product to be sold, bartered, or exchanged or offered, sent, carried or brought for sale, barter, or exchange;

(vii) Summaries of results of tests performed on the lot(s) represented by the submitted samples; and

(viii) Specimens of the labels, enclosures, and containers proposed to be used for the product.

(2) An application for license shall not be considered as filed until all pertinent information and data have been received from the applicant by the Center for Biologics Evaluation and Research. The applicant shall also include either a claim for categorical exclusion under §25.30 or 25.31 of this chapter or an environmental assessment under §25.40 of this chapter.

(3) Approval of the biologics license application and issuance of the biologics license shall constitute a determination that the establishment and the product meet applicable standards established in this chapter to ensure the continued safety, purity, and potency of such products. Applicable standards for the maintenance of establishments for the manufacture of a product subject to this paragraph (c) shall include the good manufacturing practice requirements set forth in parts 210 and 211 of this chapter. The following sections in parts 600 through 680 of this chapter shall not be applicable to such products: §§600.10(b) and (c), 600.11, 600.12, 600.13, 601.1, 610.11, 610.53, and 610.62 of this chapter.

(4) The term ''product license application,'' as it is used in those sections of parts 600 through 680 of this chapter that are applicable to products subject to this paragraph (c) shall include a biologics license application for a therapeutic DNA plasmid product, therapeutic synthetic peptide product of 40 or fewer amino acids, monoclonal antibody product for in vivo use, or therapeutic recombinant DNA-derived product.

(5) To the extent that the requirements in this paragraph (c) conflict with other requirements in this subchapter, this paragraph (c) shall supersede such other requirements.

(6) The applicant, or the applicant's attorney, agent, or other authorized official shall sign the application.

[40 FR 31313, July 25, 1975, as amended at 46 FR 8955, Jan. 27, 1981; 47 FR 6618, Feb. 16, 1982; 49 FR 23833, June 8, 1984; 50 FR 7518, Feb. 22, 1985; 50 FR 16669, Apr. 26, 1985; 55 FR 11013 and 11014, Mar. 26, 1990; 61 FR 24232, May 14, 1996; 62 FR 11769, Mar. 13, 1997; 62 FR 40600, July 29, 1997; 62 FR 53538, Oct. 15, 1997; 63 FR 5253, Feb. 2, 1998]

EFFECTIVE DATE NOTE: At 63 FR 5253, Feb. 2, 1998, §601.2 was amended in paragraph (a) by adding a sentence after the first sentence, effective Feb. 2, 1999.

§601.3 License forms.

(a) *Establishment license.* The establishment license form shall be prescribed by the Director, Center for Biologics Evaluation and Research and shall include:

(1) The name and address of the manufacturer.

(2) The name and address of the establishment.

(3) The names and addresses of all locations of the establishment.

(4) The license number.

(5) The date of issuance.

(b) *Product license.* The product license form shall be prescribed by the

Director, Center for Biologics Evaluation and Research and shall include:

(1) The name and address of the manufacturer.

(2) The name and address of the establishment.

(3) The name and address of each location at which the product is manufactured.

(4) The license number of the establishment.

(5) The proper name of the product, with additional specifications, if any, which may be approved or required for additional labeling purposes.

[38 FR 32052, Nov. 20, 1973, as amended at 49 FR 23833, June 8, 1984; 55 FR 11013, Mar. 26, 1990]

§ 601.4 Issuance and denial of license.

(a) An establishment or product license shall be issued upon a determination by the Director, Center for Biologics Evaluation and Research that the establishment or the product, as the case may be, meets the applicable standards established in this chapter. Licenses shall be valid until suspended or revoked.

(b) If the Commissioner determines that the establishment or product does not meet the standards established in this chapter, he shall deny the application and inform the applicant of the grounds for, and of an opportunity for a hearing on, his decision. If the applicant so requests, the Commissioner shall issue a notice of opportunity for hearing on the matter pursuant to § 12.21(b) of this chapter.

[42 FR 4718, Jan. 25, 1977, as amended at 42 FR 15676, Mar. 22, 1977; 42 FR 19142, Apr. 12, 1977; 49 FR 23833, June 8, 1984; 55 FR 11013, Mar. 26, 1990]

§ 601.5 Revocation of license.

(a) An establishment or product license shall be revoked upon application of the manufacturer giving notice of intention to discontinue the manufacture of all products or to discontinue the manufacture of a particular product for which a license is held, and waiving an opportunity for a hearing on the matter.

(b) If the Commissioner finds that (1) authorized Food and Drug Administration employees after reasonable efforts have been unable to gain access to an establishment or a location for the purpose of carrying out the inspection required under § 600.21 of this chapter, (2) manufacturing of products or of a product has been discontinued to an extent that a meaningful inspection or evaluation cannot be made, (3) the manufacturer has failed to report a change as required by § 601.12, (4) the establishment or any location thereof, or the product for which the license has been issued, fails to conform to the applicable standards established in the license and in this chapter designed to ensure the continued safety, purity, and potency of the manufactured product, (5) the establishment or the manufacturing methods have been so changed as to require a new showing that the establishment or product meets the standards established in this chapter in order to protect the public health, or (6) the licensed product is not safe and effective for all of its intended uses or is misbranded with respect to any such use, he shall notify the licensee of his intention to revoke the license, setting forth the grounds for, and offering an opportunity for a hearing on, the proposed revocation. Except as provided in § 601.6 or in cases involving willfulness, the notification required in this paragraph shall provide a reasonable period for the licensee to demonstrate or achieve compliance with the requirements of this chapter, before proceedings will be instituted for the revocation of the license. If compliance is not demonstrated or achieved and the licensee does not waive the opportunity for a hearing, the Commissioner shall issue a notice of opportunity for hearing on the matter pursuant to § 12.21(b) of this chapter.

[42 FR 4718, Jan. 25, 1977, as amended at 42 FR 15676, Mar. 22, 1977; 42 FR 19143, Apr. 12, 1977; 49 FR 23833, June 8, 1984]

§ 601.6 Suspension of license.

(a) Whenever the Commissioner has reasonable grounds to believe that any of the grounds for revocation of a license exist and that by reason thereof there is a danger to health, he may notify the licensee that his license for the establishment or the product is suspended and require that the licensee (1) notify the selling agents and distributors to whom such product or products

have been delivered of such suspension, and (2) furnish to the Director, Center for Biologics Evaluation and Research, complete records of such deliveries and notice of suspension.

(b) Upon suspension of a license, the Commissioner shall either (1) proceed pursuant to the provisions of § 601.5(b) to revoke the license, or (2) if the licensee agrees, hold revocation in abeyance pending resolution of the matters involved.

[42 FR 4718, Jan. 25, 1977 as amended at 49 FR 23833, June 8, 1984; 55 FR 11013, Mar. 26, 1990]

§ 601.7 Procedure for hearings.

(a) A notice of opportunity for hearing, notice of appearance and request for hearing, and grant or denial of hearing for a biological drug pursuant to this part, for which the exemption from the Federal Food, Drug, and Cosmetic Act in § 310.4 of this chapter has been revoked, shall be subject to the provisions of § 314.200 of this chapter except to the extent that the notice of opportunity for hearing on the matter issued pursuant to § 12.21(b) of this chapter specifically provides otherwise.

(b) Hearings pursuant to §§ 601.4 through 601.6 shall be governed by part 12 of this chapter.

(c) When a license has been suspended pursuant to § 601.6 and a hearing request has been granted, the hearing shall proceed on an expedited basis.

[42 FR 4718, Jan. 25, 1977, as amended at 42 FR 15676, Mar. 22, 1977; 42 FR 19143, Apr. 12, 1977]

§ 601.8 Publication of revocation.

Notice of revocation of a license, with statement of the cause therefor, shall be issued by the Commissioner and published in the FEDERAL REGISTER.

[42 FR 4718, Jan. 25, 1977]

§ 601.9 Licenses; reissuance.

(a) *Compliance with standards.* An establishment or product license, previously suspended or revoked, may be reissued or reinstated upon a showing of compliance with required standards and upon such inspection and examination as may be considered necessary by the Director, Center for Biologics Evaluation and Research.

(b) *Exclusion of noncomplying location.* An establishment or product license, excluding a location or locations that fail to comply with required standards, may be issued without further application and concurrently with the suspension or revocation of the license for noncompliance at the excluded location or locations.

[42 FR 4718, Jan. 25, 1977, as amemded at 49 FR 23833, June 8, 1984; 55 FR 11013, Mar. 26, 1990]

Subpart B—Establishment Licensing

§ 601.10 Establishment licenses; issuance and conditions.

(a) *Inspection—compliance with standards.* An establishment license shall be issued only after inspection of the establishment and upon a determination that the establishment complies with the applicable standards prescribed in the regulations in this subchapter.

(b) *Availability of product; simultaneous request for and issuance of product license.* No establishment license shall be issued unless (1) a product intended for sale, barter or exchange or intended to be offered, sent, carried or brought for sale, barter or exchange is available for examination, (2) such product is available for inspection during all phases of manufacture and (3) a product license is requested and issued simultaneously with the establishment license.

(c) *One establishment license to cover all locations.* One establishment license shall be issued to cover all locations meeting the establishment standards.

§ 601.12 Changes to an approved application.

(a) *General.* As provided by this section, an applicant shall inform Food and Drug Administration (FDA) about each change in the product, production process, quality controls, equipment, facilities, responsible personnel, or labeling, established in the approved license application(s). Before distributing a product made using a change, an applicant shall demonstrate through appropriate validation and/or other clinical and/or non-clinical laboratory studies, the lack of adverse effect of the change on the identity, strength,

quality, purity, or potency of the product as they may relate to the safety or effectiveness of the product.

(b) *Changes requiring supplement submission and approval prior to distribution of the product made using the change (major changes).* (1) A supplement shall be submitted for any change in the product, production process, quality controls, equipment, facilities, or responsible personnel that has a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of the product as they may relate to the safety or effectiveness of the product.

(2) These changes include, but are not limited to:

(i) Changes in the qualitative or quantitative formulation or other specifications as provided in the approved application or in the regulations;

(ii) Changes requiring completion of an appropriate human study to demonstrate the equivalence of the identity, strength, quality, purity, or potency of the product as they may relate to the safety or effectiveness of the product;

(iii) Changes in the virus or adventitious agent removal or inactivation method(s);

(iv) Changes in the source material or cell line;

(v) Establishment of a new master cell bank or seed; and

(vi) Changes which may affect product sterility assurance, such as changes in product or component sterilization method(s), or an addition, deletion, or substitution of steps in an aseptic processing operation.

(3) The applicant must obtain approval of the supplement from FDA prior to distribution of the product made using the change. Except for submissions under paragraph (e) of this section, the following shall be contained in the supplement:

(i) A detailed description of the proposed change;

(ii) The product(s) involved;

(iii) The manufacturing site(s) or area(s) affected;

(iv) A description of the methods used and studies performed to evaluate the effect of the change on the identity, strength, quality, purity, or potency of the product as they may relate to the safety or effectiveness of the product;

(v) The data derived from such studies;

(vi) Relevant validation protocols and data; and

(vii) A reference list of relevant standard operating procedures (SOP's).

(c) *Changes requiring supplement submission at least 30 days prior to distribution of the product made using the change.* (1) A supplement shall be submitted for any change in the product, production process, quality controls, equipment, facilities, or responsible personnel that has a moderate potential to have an adverse effect on the identity, strength, quality, purity, or potency of the product as they may relate to the safety or effectiveness of the product. The supplement shall be labeled ''Supplement—Changes Being Effected in 30 Days'' or, if applicable under paragraph (c)(5) of this section, ''Supplement—Changes Being Effected.''

(2) These changes include, but are not limited to:

(i) Change in the site of testing from one facility to another;

(ii) An increase or decrease in production scale during finishing steps that involves new or different equipment; and

(iii) Replacement of equipment with that of similar, but not identical, design and operating principle that does not affect the process methodology or process operating parameters.

(3) Pending approval of the supplement by FDA, and except as provided in paragraph (c)(5) of this section, distribution of the product made using the change may begin not less than 30 days after receipt of the supplement by FDA. The information listed in paragraph (b)(3)(i) through (b)(3)(vii) of this section shall be contained in the supplement.

(4) If within 30 days following FDA's receipt of the supplement, FDA informs the applicant that either:

(i) The change requires approval prior to distribution of the product in accordance with paragraph (b) of this section; or

(ii) Any of the information required under paragraph (c)(3) of this section is

missing; the applicant shall not distribute the product made using the change until FDA determines that compliance with this section is achieved.

(5) In certain circumstances, FDA may determine that, based on experience with a particular type of change, the supplement for such change is usually complete and provides the proper information, and on particular assurances that the proposed change has been appropriately submitted, the product made using the change may be distributed immediately upon receipt of the supplement by FDA. These circumstances may include substantial similarity with a type of change regularly involving a ''Supplement—Changes Being Effected'' supplement or a situation in which the applicant presents evidence that the proposed change has been validated in accordance with an approved protocol for such change under paragraph (e) of this section.

(d) *Changes to be described in an annual report (minor changes).* (1) Changes in the product, production process, quality controls, equipment, facilities, or responsible personnel that have a minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of the product as they may relate to the safety or effectiveness of the product shall be documented by the applicant in an annual report submitted each year within 60 days of the anniversary date of approval of the application. The Director, Center for Biologics Evaluation and Research, may approve a written request for an alternative date to combine annual reports for multiple approved applications into a single annual report submission.

(2) These changes include, but are not limited to:

(i) Any change made to comply with an official compendium that is consistent with FDA requirements;

(ii) The deletion of an ingredient intended only to affect the color of the product except that a change intended only to affect Blood Grouping Reagents requires supplement submission and approval prior to distribution of the product made using the change in accordance with the requirements set forth in paragraph (b) of this section;

(iii) An extension of an expiration date based upon full shelf-life data obtained from a protocol approved in the application;

(iv) A change within the container and closure system for solid dosage forms, based upon a showing of equivalency to the approved system under a protocol approved in the application or published in an official compendium;

(v) A change in the size of a container for a solid dosage form, without a change from one container and closure system to another;

(vi) The addition by embossing, debossing, or engraving of a code imprint to a solid dosage form biological product other than a modified release dosage form, or a minor change in an existing code imprint; and

(vii) The addition or deletion of an alternate analytical method.

(3) The following information for each change shall be contained in the annual report:

(i) A list of all products involved; and

(ii) A full description of the manufacturing and controls changes including: the manufacturing site(s) or area(s) involved; the date the change was made; a cross-reference to relevant validation protocols and/or SOP's; and relevant data from studies and tests performed to evaluate the effect of the change on the identity, strength, quality, purity, or potency of the product as they may relate to the safety or effectiveness of the product.

(4) The applicant shall submit the report to the FDA office responsible for reviewing the application. The report shall include all the information required under this paragraph for each change made during the annual reporting interval which ends on the anniversary date in the order in which they were implemented.

(e) An applicant may submit one or more protocols describing the specific tests and validation studies and acceptable limits to be achieved to demonstrate the lack of adverse effect for specified types of manufacturing changes on the identity, strength, quality, purity, or potency of the product as they may relate to the safety or effectiveness of the product. Any such

protocols, or change to a protocol, shall be submitted as a supplement requiring approval from FDA prior to distribution of the product which, if approved, may justify a reduced reporting category for the particular change because the use of the protocol for that type of change reduces the potential risk of an adverse effect.

(f) *Labeling changes.* (1) Labeling changes requiring supplement submission—FDA approval must be obtained before distribution of the product with the labeling change. Except as described in paragraphs (f)(2) and (f)(3) of this section, an applicant shall submit a supplement describing a proposed change in the package insert, package label, or container label, and include the information necessary to support the proposed change. The supplement shall clearly highlight the proposed change in the labeling. The applicant shall obtain approval from FDA prior to distribution of the product with the labeling change.

(2) *Labeling changes requiring supplement submission—product with a labeling change that may be distributed before FDA approval.* (i) An applicant shall submit, at the time such change is made, a supplement for any change in the package insert, package label, or container label to accomplish any of the following:

(A) To add or strengthen a contraindication, warning, precaution, or adverse reaction;

(B) To add or strengthen a statement about abuse, dependence, psychological effect, or overdosage;

(C) To add or strengthen an instruction about dosage and administration that is intended to increase the safety of the use of the product; and

(D) To delete false, misleading, or unsupported indications for use or claims for effectiveness.

(ii) Pending approval of the supplement by FDA, the applicant may distribute a product with a package insert, package label, or container label bearing such change at the time the supplement is submitted. The supplement shall clearly identify the change being made and include necessary supporting data. The supplement and its mailing cover shall be plainly marked: ''Special Labeling Supplement—Changes Being Effected.''

(3) *Labeling changes requiring submission in an annual report.* (i) An applicant shall submit any final printed package insert, package label, or container label incorporating the following changes in an annual report submitted to FDA each year as provided in paragraph (d)(1) of this section:

(A) Editorial or similar minor changes; and

(B) A change in the information on how the product is supplied that does not involve a change in the dosage strength or dosage form.

(ii) The applicant may distribute a product with a package insert, package label, or container label bearing such change at the time the change is made.

(4) *Advertisements and promotional labeling.* Advertisements and promotional labeling shall be submitted to the Center for Biologics Evaluation and Research in accordance with the requirements set forth in § 314.81(b)(3)(i) of this chapter, except that Form FDA–2567 (Transmittal of Labels and Circulars) or an equivalent form shall be used.

(g) *Failure to comply.* In addition to other remedies available in law and regulations, in the event of repeated failure of the applicant to comply with this section, FDA may require that the applicant submit a supplement for any proposed change and obtain approval of the supplement by FDA prior to distribution of the product made using the change.

(h) *Administrative review.* Under § 10.75 of this chapter, an applicant may request internal FDA review of FDA employee decisions under this section.

[62 FR 39901, July 24, 1997]

Subpart C—Product Licensing

§ 601.20 Product licenses; issuance and conditions.

(a) *Examination—compliance with standards.* A product license shall be issued only upon examination of the product and upon a determination that the product complies with the standards prescribed in the regulations in this subchapter: *Provided,* That no product license shall be issued except

upon a determination that the establishment complies with the establishment standards prescribed in the regulations contained in this subchapter, applicable to the manufacture of such product.

(b) *Manufacturing process—impairment of assurances.* No product shall be licensed if any part of the process of or relating to the manufacture of such product, in the judgment of the Commissioner of Food and Drugs, would impair the assurances of continued safety, purity and potency as provided by the regulations contained in this subchapter.

§ 601.21 Products under development.

A biological product undergoing development, but not yet ready for a product license, may be shipped or otherwise delivered from one State or possession into another State or possession provided such shipment or delivery is not for sale, barter, or exchange, except as provided in section 505(i) of the Federal Food, Drug, and Cosmetic Act, as amended, and the regulations thereunder (21 CFR part 312).

[45 FR 73923, Nov. 7, 1980, as amended at 55 FR 11014, Mar. 26, 1990]

§ 601.22 Products in short supply; initial manufacturing at other than licensed establishment.

Licenses issued to a manufacturer for an establishment shall authorize persons other than such manufacturer to conduct at places other than such establishment the initial, and partial manufacturing of a product for shipment solely to such manufacturer only to the extent that the names of such persons and places are registered with the Commissioner of Food and Drugs and he finds upon application of such manufacturer, that (a) the product is in short supply due either to the peculiar growth requirements of the organism involved or to the scarcity of the animal required for manufacturing purposes, and (b) such manufacturer has established with respect to such persons and places such procedures, inspections, tests or other arrangements as will assure full compliance with the applicable regulations of this subchapter related to continued safety, purity, and potency. Such persons and places shall be subject to all regulations of this subchapter except §§ 601.1 to 601.6, 601.9, 601.10, 601.20, 601.21, 601.30 to 601.33, and §§610.60 to 610.65 of this chapter. For persons and places authorized under this section to conduct the initial and partial manufacturing of a product for shipment solely to a manufacturer of a product subject to licensure under § 601.2(c), the following additional regulations shall not be applicable: §§ 600.10(b) and (c), 600.11, 600.12, 600.13, 610.11, and 610.53 of this chapter. Failure of such manufacturer to maintain such procedures, inspections, tests, or other arrangements, or failure of any person conducting such partial manufacturing to comply with applicable regulations shall constitute a ground for suspension or revocation of the authority conferred pursuant to this section on the same basis as provided in §§ 601.6 to 601.8 with respect to the suspension and the revocation of licenses.

[42 FR 4718, Jan. 25, 1977, as amended at 61 FR 24233, May 14, 1996]

§ 601.25 Review procedures to determine that licensed biological products are safe, effective, and not misbranded under prescribed, recommended, or suggested conditions of use.

For purposes of reviewing biological products that have been licensed prior to July 1, 1972, to determine that they are safe and effective and not misbranded, the following regulations shall apply. Prior administrative action exempting biological products from the provisions of the Federal Food, Drug, and Cosmetic Act is superseded to the extent that these regulations result in imposing requirements pursuant to provisions therein for a designated biological product or category of products.

(a) *Advisory review panels.* The Commissioner of Food and Drugs shall appoint advisory review panels (1) to evaluate the safety and effectiveness of biological products for which a license has been issued pursuant to section 351 of the Public Health Service Act, (2) to review the labeling of such biological products, and (3) to advise him on which of the biological products under

review are safe, effective, and not misbranded. An advisory review panel shall be established for each designated category of biological product. The members of a panel shall be qualified experts, appointed by the Commissioner, and shall include persons from lists submitted by organizations representing professional, consumer, and industry interests. Such persons shall represent a wide divergence of responsible medical and scientific opinion. The Commissioner shall designate the chairman of each panel, and summary minutes of all meetings shall be made.

(b) *Request for data and views.* (1) The Commissioner of Food and Drugs will publish a notice in the FEDERAL REGISTER requesting interested persons to submit, for review and evaluation by an advisory review panel, published and unpublished data and information pertinent to a designated category of biological products.

(2) Data and information submitted pursuant to a published notice, and falling within the confidentiality provisions of 18 U.S.C. 1905, 5 U.S.C. 552(b), or 21 U.S.C. 331(j), shall be handled by the advisory review panel and the Food and Drug Administration as confidential until publication of a proposed evaluation of the biologics under review and the full report or reports of the panel. Thirty days thereafter such data and information shall be made publicly available and may be viewed at the Dockets Management Branch of the Food and Drug Administration, except to the extent that the person submitting it demonstrates that it still falls within the confidentiality provisions of one or more of those statutes.

(3) To be considered, 12 copies of the submission on any marketed biological product within the class shall be submitted, preferably bound, indexed, and on standard sized paper, approximately 8½ × 11 inches. The time allotted for submissions will be 60 days, unless otherwise indicated in the specific notice requesting data and views for a particular category of biological products. When requested, abbreviated submissions should be sent. All submissions shall be in the following format, indicating ''none'' or ''not applicable'' where appropriate, unless changed in the FEDERAL REGISTER notice:

BIOLOGICAL PRODUCTS REVIEW INFORMATION

I. Label or labels and all other labeling (preferably mounted. Facsimile labeling is acceptable in lieu of actual container labeling), including labeling for export.

II. Representative advertising used during the past 5 years.

III. The complete quantitative composition of the biological product.

IV. Animal safety data.

A. Individual active components.

1. Controlled studies.

2. Partially controlled or uncontrolled studies.

B. Combinations of the individual active components.

1. Controlled studies.

2. Partially controlled or uncontrolled studies.

C. Finished biological product.

1. Controlled studies.

2. Partially controlled or uncontrolled studies.

V. Human safety data.

A. Individual active components.

1. Controlled studies.

2. Partially controlled or uncontrolled studies.

3. Documented case reports.

4. Pertinent marketing experiences that may influence a determination as to the safety of each individual active component.

5. Pertinent medical and scientific literature.

B. Combinations of the individual active components.

1. Controlled studies.

2. Partially controlled or uncontrolled studies.

3. Documented case reports.

4. Pertinent marketing experiences that may influence a determination as to the safety of combinations of the individual active components.

5. Pertinent medical and scientific literature.

C. Finished biological product.

1. Controlled studies.

2. Partially controlled or uncontrolled studies.

3. Documented case reports.

4. Pertinent marketing experiences that may influence a determination as to the safety of the finished biological product.

5. Pertinent medical and scientific literature.

VI. Efficacy data.

A. Individual active components.

1. Controlled studies.

2. Partially controlled or uncontrolled studies.

3. Documented case reports.

4. Pertinent marketing experiences that may influence a determination on the efficacy of each individual active component.

5. Pertinent medical and scientific literature.

B. Combinations of the individual active components.

1. Controlled studies.

2. Partially controlled or uncontrolled studies.

3. Documented case reports.

4. Pertinent marketing experiences that may influence a determination as to the effectiveness of combinations of the individual active components.

5. Pertinent medical and scientific literature.

C. Finished biological product.

1. Controlled studies.

2. Partially controlled or uncontrolled studies.

3. Documented case reports.

4. Pertinent marketing experiences that may influence a determination as to the effectiveness of the finished biological product.

5. Pertinent medical and scientific literature.

VII. A summary of the data and views setting forth the medical rational and purpose (or lack thereof) for the biological product and its components and the scientific basis (or lack thereof) for the conclusion that the biological product, including its components, has been proven safe and effective and is properly labeled for the intended use or uses. If there is an absence of controlled studies in the materials submitted, an explanation as to why such studies are not considered necessary or feasible shall be included.

VIII. If the submission is by a licensee, a statement signed by an authorized official of the licensee shall be included, stating that to the best of his or her knowledge and belief, it includes all information, favorable and unfavorable, pertinent to an evaluation of the safety, effectiveness, and labeling of the product, including information derived from investigation, commercial marketing, or published literature. If the submission is by an interested person other than a licensee, a statement signed by the person responsible for such submission shall be included, stating that to the best of his knowledge and belief, it fairly reflects a balance of all the information, favorable and unfavorable, available to him pertinent to an evaluation of the safety, effectiveness, and labeling of the product.

(c) *Deliberations of an advisory review panel.* An advisory review panel will meet as often and for as long as is appropriate to review the data submitted to it and to prepare a report containing its conclusions and recommendations to the Commissioner of Food and Drugs with respect to the safety, effectiveness, and labeling of the biological products in the designated category under review.

(1) A panel may also consult any individual or group.

(2) Any interested person may request in writing an opportunity to present oral views to the panel. Such written requests for oral presentations should include a summarization of the data to be presented to the panel. Such request may be granted or denied by the panel.

(3) Any interested person may present written data and views which shall be considered by the panel. This information shall be presented to the panel in the format set forth in paragraph (b)(3) of this section and within the time period established for the biological product category in the notice for review by a panel.

(d) *Standards for safety, effectiveness, and labeling.* The advisory review panel, in reviewing the submitted data and preparing the panel's conclusions and recommendations, and the Commissioner of Food and Drugs, in reviewing and implementing the conclusions and recommendations of the panel, shall apply the following standards to determine that a biological product is safe and effective and not misbranded.

(1) Safety means the relative freedom from harmful effect to persons affected, directly or indirectly, by a product when prudently administered, taking into consideration the character of the product in relation to the condition of the recipient at the time. Proof of safety shall consist of adequate tests by methods reasonably applicable to show the biological product is safe under the prescribed conditions of use, including results of significant human experience during use.

(2) Effectiveness means a reasonable expectation that, in a significant proportion of the target population, the pharmacological or other effect of the biological product, when used under adequate directions, for use and warnings against unsafe use, will serve a clinically significant function in the diagnosis, cure, mitigation, treatment, or prevention of disease in man. Proof of effectiveness shall consist of controlled clinical investigations as defined in § 314.126 of this chapter, unless this requirement is waived on the basis of a showing that it is not reasonably applicable to the biological product or

essential to the validity of the investigation, and that an alternative method of investigation is adequate to substantiate effectiveness. Alternate methods, such as serological response evaluation in clinical studies and appropriate animal and other laboratory assay evaluations may be adequate to substantiate effectiveness where a previously accepted correlation between data generated in this way and clinical effectiveness already exists. Investigations may be corroborated by partially controlled or uncontrolled studies, documented clinical studies by qualified experts, and reports of significant human experience during marketing. Isolated case reports, random experience, and reports lacking the details which permit scientific evaluation will not be considered.

(3) The benefit-to-risk ratio of a biological product shall be considered in determining safety and effectiveness.

(4) A biological product may combine two or more safe and effective active components: (i) When each active component makes a contribution to the claimed effect or effects; (ii) when combining of the active ingredients does not decrease the purity, potency, safety, or effectiveness of any of the individual active components; and (iii) if the combination, when used under adequate directions for use and warnings against unsafe use, provides rational concurrent preventive therapy or treatment for a significant proportion of the target population.

(5) Labeling shall be clear and truthful in all respects and may not be false or misleading in any particular. It shall comply with section 351 of the Public Health Service Act and sections 502 and 503 of the Federal Food, Drug, and Cosmetic Act, and in particular with the applicable requirements of §§ 610.60 through 610.65 and subpart D of part 201 of this chapter.

(e) *Advisory review panel report to the Commissioner.* An advisory review panel shall submit to the Commissioner of Food and Drugs a report containing the panel's conclusions and recommendations with respect to the biological products falling within the category covered by the panel. Included within this report shall be:

(1) A statement which designates those biological products determined by the panel to be safe and effective and not misbranded. This statement may include any condition relating to active components, labeling, tests required prior to release of lots, product standards, or other conditions necessary or appropriate for their safety and effectiveness.

(2) A statement which designates those biological products determined by the panel to be unsafe or ineffective, or to be misbranded. The statement shall include the panel's reasons for each such determination.

(3) A statement which designates those biological products determined by the panel not to fall within either paragraph (e) (1) or (2) of this section on the basis of the panel's conclusion that the available data are insufficient to classify such biological products, and for which further testing is therefore required. The report shall recommend with as must specificity as possible the type of further testing required and the time period within which it might reasonably be concluded. The report shall also recommend whether the product license should or should not be revoked, thus permitting or denying continued manufacturing and marketing of the biological product pending completion of the testing. This recommendation will be based on an assessment of the present evidence of the safety and effectiveness of the product and the potential benefits and risks likely to result from the continued use of the product for a limited period of time while the questions raised concerning the product are being resolved by further study.[2]

(f) *Proposed order.* After reviewing the conclusions and recommendations of the advisory review panel, the Commissioner of Food and Drugs shall publish in the FEDERAL REGISTER a proposed order containing:

[2] As of November 4, 1982, the provisions under paragraphs (e)(3) and (f)(3) of this section for the interim marketing of certain biological products pending completion of additional studies have been superseded by the review and reclassification procedures under § 601.26 of this chapter. The superseded text is included for the convenience of the user only.

(1) A statement designating the biological products in the category under review that are determined by the Commissioner of Food and Drugs to be safe and effective and not misbranded. This statement may include any condition relating to active components, labeling, tests required prior to release of lots, product standards, or other conditions necessary or appropriate for their safety and effectiveness, and may propose corresponding amendments in other regulations under this subchapter F.

(2) A statement designating the biological products in the category under review that are determined by the Commissioner of Food and Drugs to be unsafe or ineffective, or to be misbranded, together with the reasons therefor. All licenses for such products shall be proposed to be revoked.

(3) A statement designating the biological products not included in either of the above two statements on the basis of the Commissioner of Food and Drugs determination that the available data are insufficient to classify such biological products under either paragraph (f) (1) or (2) of this section. Licenses for such products may be proposed to be revoked or to remain in effect on an interim basis. Where the Commissioner determines that the potential benefits outweigh the potential risks, the proposed order shall provide that the product license for any biological product, falling within this paragraph will not be revoked but will remain in effect on an interim basis while the data necessary to support its continued marketing are being obtained for evaluation by the Food and Drug Administration. The tests necessary to resolve whatever safety or effectiveness questions exist shall be described.[2]

(4) The full report or reports of the panel to the Commissioner of Food and Drugs.

[2] As of November 4, 1982, the provisions under paragraphs (e)(3) and (f)(3) of this section for the interim marketing of certain biological products pending completion of additional studies have been superseded by the review and reclassification procedures under § 601.26 of this chapter. The superseded text is included for the convenience of the user only.

The summary minutes of the panel meeting or meetings shall be made available to interested persons upon request. Any interested person may within 90 days after publication of the proposed order in the FEDERAL REGISTER, file with the Hearing Clerk of the Food and Drug Administration written comments in quintuplicate. Comments may be accompanied by a memorandum or brief in support thereof. All comments may be reviewed at the office of the Dockets Management Branch during regular working hours, Monday through Friday.

(g) *Final order.* After reviewing the comments, the Commissioner of Food and Drugs shall publish in the FEDERAL REGISTER a final order on the matters covered in the proposed order. The final order shall become effective as specified in the order.

(h) [Reserved]

(i) *Court Appeal.* The final order(s) published pursuant to paragraph (g) of this section, and any notice published pursuant to paragraph (h) of this section, constitute final agency action from which appeal lies to the courts. The Food and Drug Administration will request consolidation of all appeals in a single court. Upon court appeal, the Commissioner of Food and Drugs may, at his discretion, stay the effective date for part or all of the final order or notice, pending appeal and final court adjudication.

[38 FR 32052, Nov. 20, 1973, as amended at 39 FR 11535, Mar. 29, 1974; 40 FR 13498, Mar. 27, 1975; 43 FR 44838, Sept. 29, 1978; 47 FR 44071, Oct. 5, 1982; 47 FR 50211, Nov. 5, 1982; 51 FR 15607, Apr. 25, 1986; 55 FR 11014, Mar. 26, 1990; 62 FR 53538, Oct. 15, 1997]

§ 601.26 Reclassification procedures to determine that licensed biological products are safe, effective, and not misbranded under prescribed, recommended, or suggested conditions of use.

This regulation establishes procedures for the reclassification of all biological products that have been classified into Category IIIA. A Category IIIA biological product is one for which an advisory review panel has recommended under § 601.25(e)(3), the Commissioner of Food and Drugs (Commissioner) has proposed under § 601.25(f)(3), or the Commissioner has finally decided under § 601.25(g) that available data are insufficient to determine whether the product license should be

revoked or affirmed and which may be marketed pending the completion of further testing. All of these Category IIIA products will either be reclassified into Category I (safe, effective, and not misbranded) or Category II (unsafe, ineffective, or misbranded) in accordance with the procedures set forth below.

(a) *Advisory review panels.* The Commissioner will appoint advisory review panels and use existing advisory review panels to (1) evaluate the safety and effectiveness of all Category IIIA biological products; (2) review the labeling of such products; and (3) advise the Commissioner on which Category IIIA biological products are safe, effective, and not misbranded. These advisory review panels will be established in accordance with procedures set forth in § 601.25(a).

(b) *Deliberations of advisory review panels.* The deliberations of advisory review panels will be conducted in accordance with § 601.25(d).

(c) *Advisory review panel report to the Commissioner.* An advisory review panel shall submit to the Commissioner a report containing the panel's conclusions and recommendations with respect to the biological products falling within the category of products reviewed by the panel. The panel report shall include:

(1) A statement designating the biological products in the category under review in accordance with either § 601.25(e)(1) or § 601.25(e)(2).

(2) A statement identifying those biological products designated under § 601.25(e)(2) that the panel recommends should be designated as safe and presumptively effective and should remain on the market pending completion of further testing because there is a compelling medical need and no suitable alternative therapeutic, prophylactic, or diagnostic agent that is available in sufficient quantities to meet current medical needs. For the products or categories of products so recommended, the report shall include:

(i) A description and evaluation of the available evidence concerning effectiveness and an explanation why the evidence shows that the product has any benefit; and

(ii) A description of the alternative therapeutic, prophylactic, or diagnostic agents considered and a statement of why such alternatives are not suitable. In making this recommendation the panel shall also take into account the seriousness of the condition intended to be treated, prevented, or diagnosed by the product, the risks involved in the continued use of the product, and the likelihood that, based upon existing data, the effectiveness of the product can eventually be established by further testing and new test development. The report shall also recommend with as much specificity as possible the type of further testing required and the time period within which it might reasonably be concluded.

(d) *Proposed order.* After reviewing the conclusions and recommendations of the advisory review panels, the Commissioner shall publish in the FEDERAL REGISTER a proposed order containing:

(1) A statement designating the biological products in the category under review in accordance with either § 601.25(e)(1) or 601.25(e)(2);

(2) A notice of availability of the full panel report or reports. The full panel report or reports shall be made publicly available at the time of publication of the proposed order.

(3) A proposal to accept or reject the findings of the advisory review panel required by § 601.26(c)(2)(i) and (ii).

(4) A statement identifying those biological products that the Commissioner proposes should be designated as safe and presumptively effective under § 601.26(c)(2) and should be permitted to remain on the market pending completion of further testing because there is a compelling medical need and no suitable alternative therapeutic, prophylactic, or diagnostic agent for the product that is available in sufficient quantities to meet current medical needs. In making this proposal, the Commissioner shall take into account the seriousness of the condition to be treated, prevented, or diagnosed by the product, the risks involved in the continued use of the product, and the likelihood that, based upon existing data, the effectiveness of the product can eventually be established by further testing.

(e) *Final order.* After reviewing the comments on the proposed order, the

Commissioner shall publish in the FEDERAL REGISTER a final order on the matters covered in the proposed order. Where the Commissioner determines that there is a compelling medical need and no suitable alternative therapeutic, prophylactic, or diagnostic agent for any biological product that is available in sufficient quantities to meet current medical needs, the final order shall provide that the product license for that biological product will not be revoked, but will remain in effect on an interim basis while the data necessary to support its continued marketing are being obtained for evaluation by the Food and Drug Administration. The final order shall describe the tests necessary to resolve whatever effectiveness questions exist.

(f) *Additional studies and labeling.* (1) Within 60 days following publication of the final order, each licensee for a biological product designated as requiring further study to justify continued marketing on an interim basis, pursuant to paragraph (e) of this section, shall submit to the Commissioner a written statement intended to show that studies adequate and appropriate to resolve the questions raised about the product have been undertaken. The Federal Government may undertake the studies. Any study involving a clinical investigation that involves human subjects shall be conducted in compliance with the requirements for informed consent under part 50 of this chapter. Such a study is also subject to the requirements for institutional review under part 56 of this chapter unless exempt under § 56.104 or § 56.105. The Commissioner may extend this 60-day period if necessary, either to review and act on proposed protocols or upon indication from the licensee that the studies will commence at a specified reasonable time. If no such commitment is made, or adequate and appropriate studies are not undertaken, the product license or licenses shall be revoked.

(2) A progress report shall be filed on the studies by January 1 and July 1 until completion. If the progress report is inadequate or if the Commissioner concludes that the studies are not being pursued promptly and diligently, or if interim results indicate the product is not a medical necessity, the product license or licenses shall be revoked.

(3) Promptly upon completion of the studies undertaken on the product, the Commissioner will review all available data and will either retain or revoke the product license or licenses involved. In making this review the Commissioner may again consult the advisory review panel which prepared the report on the product, or other advisory committees, professional organizations, or experts. The Commissioner shall take such action by notice published in the FEDERAL REGISTER.

(4) Labeling and promotional material for those biological products requiring additional studies shall bear a box statement in the following format:

> Based on a review by the (*insert name of appropriate advisory review panel*) and other information, the Food and Drug Administration has directed that further investigation be conducted before this product is conclusively determined to be effective for labeled indication(s).

(5) A written informed consent shall be obtained from participants in any additional studies required under paragraph (f)(1) of this section, explaining the nature of the product and the investigation. The explanation shall consist of such disclosure and be made so that intelligent and informed consent be given and that a clear opportunity to refuse is presented.

(g) *Court appeal.* The final order(s) published pursuant to paragraph (e) of this section constitute final agency action from which appeal lies to the courts. The Food and Drug Administration will request consolidation of all appeals in a single court. Upon court appeal, the Commissioner of Food and Drugs may, at the Commissioner's discretion, stay the effective date for part or all of the final order or notice, pending appeal and final court adjudication.

(h) [Reserved]

(i) *Institutional review and informed consent.* Information and data submitted under this section after July 27,

1981, shall include statements regarding each clinical investigation involving human subjects, that it was conducted in compliance with the requirements for informed consent under part 50 of this chapter. Such a study is also subject to the requirements for institutional review under part 56 of this chapter, unless exempt under § 56.104 or § 56.105.

[47 FR 44071, Oct. 5, 1982]

Subpart D—Licensing of Foreign Establishments and Products

§ 601.33 Samples for each importation.

Random samples of each importation, obtained by the District Director of Customs and forwarded to the Director, Center for Biologics Evaluation and Research, shall be at least two final containers of each lot of product. A copy of the associated documents which describe and identify the shipment shall accompany the shipment for forwarding with the samples to the Director, Center for Biologics Evaluation and Research. For shipments of 20 or less final containers, samples need not be forwarded, provided a copy of an official release from the Center for Biologics Evaluation and Research accompanies each shipment.

[38 FR 32052, Nov. 20, 1973, as amended at 49 FR 23833, June 8, 1984; 55 FR 11013, Mar. 26, 1990]

Subpart E—Accelerated Approval of Biological Products for Serious or Life-Threatening Illnesses

SOURCE: 57 FR 58959, Dec. 11, 1992, unless otherwise noted.

§ 601.40 Scope.

This subpart applies to certain biological products that have been studied for their safety and effectiveness in treating serious or life-threatening illnesses and that provide meaningful therapeutic benefit to patients over existing treatments (e.g., ability to treat patients unresponsive to, or intolerant of, available therapy, or improved patient response over available therapy).

§ 601.41 Approval based on a surrogate endpoint or on an effect on a clinical endpoint other than survival or irreversible morbidity.

FDA may grant marketing approval for a biological product on the basis of adequate and well-controlled clinical trials establishing that the biological product has an effect on a surrogate endpoint that is reasonably likely, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, to predict clinical benefit or on the basis of an effect on a clinical endpoint other than survival or irreversible morbidity. Approval under this section will be subject to the requirement that the applicant study the biological product further, to verify and describe its clinical benefit, where there is uncertainty as to the relation of the surrogate endpoint to clinical benefit, or of the observed clinical benefit to ultimate outcome. Postmarketing studies would usually be studies already underway. When required to be conducted, such studies must also be adequate and well-controlled. The applicant shall carry out any such studies with due diligence.

§ 601.42 Approval with restrictions to assure safe use.

(a) If FDA concludes that a biological product shown to be effective can be safely used only if distribution or use is restricted, FDA will require such postmarketing restrictions as are needed to assure safe use of the biological product, such as:

(1) Distribution restricted to certain facilities or physicians with special training or experience; or

(2) Distribution conditioned on the performance of specified medical procedures.

(b) The limitations imposed will be commensurate with the specific safety concerns presented by the biological product.

§ 601.43 Withdrawal procedures.

(a) For biological products approved under §§ 601.40 and 601.42, FDA may withdraw approval, following a hearing as provided in part 15 of this chapter, as modified by this section, if:

(1) A postmarketing clinical study fails to verify clinical benefit;

(2) The applicant fails to perform the required postmarketing study with due diligence;

(3) Use after marketing demonstrates that postmarketing restrictions are inadequate to ensure safe use of the biological product;

(4) The applicant fails to adhere to the postmarketing restrictions agreed upon;

(5) The promotional materials are false or misleading; or

(6) Other evidence demonstrates that the biological product is not shown to be safe or effective under its conditions of use.

(b) *Notice of opportunity for a hearing.* The Director of the Center for Biologics Evaluation and Research will give the applicant notice of an opportunity for a hearing on the Center's proposal to withdraw the approval of an application approved under § 601.40 or § 601.41. The notice, which will ordinarily be a letter, will state generally the reasons for the action and the proposed grounds for the order.

(c) *Submission of data and information.* (1) If the applicant fails to file a written request for a hearing within 15 days of receipt of the notice, the applicant waives the opportunity for a hearing.

(2) If the applicant files a timely request for a hearing, the agency will publish a notice of hearing in the FEDERAL REGISTER in accordance with §§ 12.32(e) and 15.20 of this chapter.

(3) An applicant who requests a hearing under this section must, within 30 days of receipt of the notice of opportunity for a hearing, submit the data and information upon which the applicant intends to rely at the hearing.

(d) *Separation of functions.* Separation of functions (as specified in § 10.55 of this chapter) will not apply at any point in withdrawal proceedings under this section.

(e) *Procedures for hearings.* Hearings held under this section will be conducted in accordance with the provisions of part 15 of this chapter, with the following modifications:

(1) An advisory committee duly constituted under part 14 of this chapter will be present at the hearing. The committee will be asked to review the issues involved and to provide advice and recommendations to the Commissioner of Food and Drugs.

(2) The presiding officer, the advisory committee members, up to three representatives of the applicant, and up to three representatives of the Center may question any person during or at the conclusion of the person's presentation. No other person attending the hearing may question a person making a presentation. The presiding officer may, as a matter of discretion, permit questions to be submitted to the presiding officer for response by a person making a presentation.

(f) *Judicial review.* The Commissioner's decision constitutes final agency action from which the applicant may petition for judicial review. Before requesting an order from a court for a stay of action pending review, an applicant must first submit a petition for a stay of action under § 10.35 of this chapter.

§ 601.44 Postmarketing safety reporting.

Biological products approved under this program are subject to the postmarketing recordkeeping and safety reporting applicable to all approved biological products.

§ 601.45 Promotional materials.

For biological products being considered for approval under this subpart, unless otherwise informed by the agency, applicants must submit to the agency for consideration during the preapproval review period copies of all promotional materials, including promotional labeling as well as advertisements, intended for dissemination or publication within 120 days following marketing approval. After 120 days following marketing approval, unless otherwise informed by the agency, the applicant must submit promotional materials at least 30 days prior to the intended time of initial dissemination of the labeling or initial publication of the advertisement.

§ 601.46 Termination of requirements.

If FDA determines after approval that the requirements established in § 601.42, § 601.43, or § 601.45 are no longer necessary for the safe and effective use of a biological product, it will so notify

the applicant. Ordinarily, for biological products approved under § 601.41, these requirements will no longer apply when FDA determines that the required postmarketing study verifies and describes the biological product's clinical benefit and the biological product would be appropriate for approval under traditional procedures. For biological products approved under § 601.42, the restrictions would no longer apply when FDA determines that safe use of the biological product can be assured through appropriate labeling. FDA also retains the discretion to remove specific postapproval requirements upon review of a petition submitted by the sponsor in accordance with § 10.30.

Subpart F—Confidentiality of Information

§ 601.50 Confidentiality of data and information in an investigational new drug notice for a biological product.

(a) The existence of an IND notice for a biological product will not be disclosed by the Food and Drug Administration unless it has previously been publicly disclosed or acknowledged.

(b) The availability for public disclosure of all data and information in an IND file for a biological product shall be handled in accordance with the provisions established in § 601.51.

(c) Notwithstanding the provisions of § 601.51, the Food and Drug Administration shall disclose upon request to an individual on whom an investigational biological product has been used a copy of any adverse reaction report relating to such use.

[39 FR 44656, Dec. 24, 1974]

§ 601.51 Confidentiality of data and information in applications for establishment and product licenses.

(a) For purposes of this section the *biological product file* includes all data and information submitted with or incorporated by reference in any application for an establishment or product license, IND's incorporated into any such application, master files, and other related submissions. The availability for public disclosure of any record in the biological product file shall be handled in accordance with the provisions of this section.

(b) The existence of a biological product file will not be disclosed by the Food and Drug Administration before a product license has been sent to the applicant, unless it has previously been publicly disclosed or acknowledged. The Director of the Center for Biologics Evaluation and Research will maintain a list available for public disclosure of biological products for which a license has been issued.

(c) If the existence of a biological product file has not been publicly disclosed or acknowledged, no data or information in the biological product file is available for public disclosure.

(d)(1) If the existence of a biological product file has been publicly disclosed or acknowledged before a license has been issued, no data or information contained in the file is available for public disclosure before such license is issued, but the Commissioner may, in his discretion, disclose a summary of such selected portions of the safety and effectiveness data as are appropriate for public consideration of a specific pending issue, e.g., at an open session of a Food and Drug Administration advisory committee or pursuant to an exchange of important regulatory information with a foreign government.

(2) Notwithstanding paragraph (d)(1) of this section, FDA will make available to the public upon request the information in the IND that was required to be filed in Docket Number 95S–0158 in the Dockets Management Branch (HFA–305), Food and Drug Administration, 12420 Parklawn Dr., rm. 1–23, Rockville, MD 20857, for investigations involving an exception from informed consent under § 50.24 of this chapter. Persons wishing to request this information shall submit a request under the Freedom of Information Act.

(e) After a license has been issued, the following data and information in the biological product file are immediately available for public disclosure unless extraordinary circumstances are shown:

(1) All safety and effectiveness data and information.

(2) A protocol for a test or study, unless it is shown to fall within the exemption established for trade secrets

and confidential commercial or financial information in §20.61 of this chapter.

(3) Adverse reaction reports, product experience reports, consumer complaints, and other similar data and information, after deletion of:

(i) Names and any information that would identify the person using the product.

(ii) Names and any information that would identify any third party involved with the report, such as a physician or hospital or other institution.

(4) A list of all active ingredients and any inactive ingredients previously disclosed to the public, as defined in §20.81 of this chapter.

(5) An assay method or other analytical method, unless it serves no regulatory or compliance purpose and it is shown to fall within the exemption established in §20.61 of this chapter.

(6) All correspondence and written summaries of oral discussions relating to the biological product file, in accordance with the provisions of part 20 of this chapter.

(7) All records showing the manufacturer's testing of a particular lot, after deletion of data or information that would show the volume of the drug produced, manufacturing procedures and controls, yield from raw materials, costs, or other material falling within §20.61 of this chapter.

(8) All records showing the testing of and action on a particular lot by the Food and Drug Administration.

(f) The following data and information in a biological product file are not available for public disclosure unless they have been previously disclosed to the public as defined in §20.81 of this chapter or they relate to a product or ingredient that has been abandoned and they no longer represent a trade secret or confidential commercial or financial information as defined in §20.61 of this chapter:

(1) Manufacturing methods or processes, including quality control procedures.

(2) Production, sales, distribution, and similar data and information, except that any compilation of such data and information aggregated and prepared in a way that does not reveal data or information which is not available for public disclosure under this provision is available for public disclosure.

(3) Quantitative or semiquantitative formulas.

(g) For purposes of this regulation, safety and effectiveness data include all studies and tests of a biological product on animals and humans and all studies and tests on the drug for identity, stability, purity, potency, and bioavailability.

[39 FR 44656, Dec. 24, 1974, as amended at 42 FR 15676, Mar. 22, 1977; 49 FR 23833, June 8, 1984; 55 FR 11013, Mar. 26, 1990; 61 FR 51530, Oct. 2, 1996]

PART 606—CURRENT GOOD MANUFACTURING PRACTICE FOR BLOOD AND BLOOD COMPONENTS

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AUTHORITY: 21 U.S.C. 321, 331, 351, 352, 355, 360, 360j, 371, 374; 42 U.S.C. 216, 262, 263a, 264.

SOURCE: 40 FR 53532, Nov. 18, 1975, unless otherwise noted.

Subpart A—General Provisions

§ 606.3 Definitions.

As used in this part:

(a) *Blood* means whole blood collected from a single donor and processed either for transfusion or further manufacturing.

(b) *Unit* means the volume of blood or one of its components in a suitable volume of anticoagulant obtained from a single collection of blood from one donor.

(c) *Component* means that part of a single-donor unit of blood separated by physical or mechanical means.

(d) *Plasma for further manufacturing* means that liquid portion of blood separated and used as material to prepare another product.

(e) *Plasmapheresis* means the procedure in which blood is removed from the donor, the plasma is separated from the formed elements and at least the red blood cells are returned to the donor. This process may be immediately repeated, once.

(f) *Plateletpheresis* means the procedure in which blood is removed from the donor, a platelet concentrate is separated, and the remaining formed elements and residual plasma are returned to the donor.

(g) *Leukapheresis* means the procedure in which blood is removed from the donor, a leukocyte concentrate is separated, and the remaining formed elements and residual plasma are returned to the donor.

(h) *Facilities* means any area used for the collection, processing, compatibility testing, storage or distribution of blood and blood components.

(i) *Processing* means any procedure employed after collection and before compatibility testing of blood and includes the identification of a unit of donor blood, the preparation of components from such unit of donor blood, serological testing, labeling and associated recordkeeping.

(j) *Compatibility testing* means the in vitro serological tests performed on donor and recipient blood samples to establish the serological matching of a donor's blood or blood components with that of a potential recipient.

Subpart B—Organization and Personnel

§ 606.20 Personnel.

(a) [Reserved]

(b) The personnel responsible for the collection, processing, compatibility testing, storage or distribution of blood or blood components shall be adequate in number, educational background, training and experience, including professional training as necessary, or combination thereof, to assure competent performance of their assigned functions, and to ensure that the final product has the safety, purity, potency, identity and effectiveness it purports or is represented to possess. All personnel shall have capabilities commensurate with their assigned functions, a thorough understanding of the procedures or control operations they perform, the necessary training or experience, and adequate information concerning the application of pertinent provisions of this part to their respective functions.

(c) Persons whose presence can adversely affect the safety and purity of the products shall be excluded from areas where the collection, processing, compatibility testing, storage or distribution of blood or blood components is conducted.

[40 FR 53532, Nov. 18, 1975, as amended at 49 FR 23833, June 8, 1984; 55 FR 11014, Mar. 26, 1990; 62 FR 53538, Oct. 15, 1997]

Subpart C—Plant and Facilities

§ 606.40 Facilities.

Facilities shall be maintained in a clean and orderly manner, and shall be of suitable size, construction and location to facilitate adequate cleaning, maintenance and proper operations. The facilities shall:

(a) Provide adequate space for the following when applicable:

(1) Private and accurate examinations of individuals to determine their suitability as blood donors.

(2) The withdrawal of blood from donors with minimal risk of contamination, or exposure to activities and equipment unrelated to blood collection.

(3) The storage of blood or blood components pending completion of tests.

(4) The quarantine storage of blood or blood components in a designated location pending repetition of those tests that initially gave questionable serological results.

(5) The storage of finished products prior to distribution.

(6) The quarantine storage, handling and disposition of products and reagents not suitable for use.

(7) The orderly collection, processing, compatibility testing, storage and distribution of blood and blood components to prevent contamination.

(8) The adequate and proper performance of all steps in plasmapheresis, plateletpheresis and leukapheresis procedures.

(9) The orderly conduction of all packaging, labeling and other finishing operations.

(b) Provide adequate lighting, ventilation and screening of open windows and doors.

(c) Provide adequate, clean, and convenient handwashing facilities for personnel, and adequate, clean, and convenient toilet facilities for donors and personnel. Drains shall be of adequate size and, where connected directly to a sewer, shall be equipped with traps to prevent back-siphonage.

(d) Provide for safe and sanitary disposal for the following:

(1) Trash and items used during the collection, processing and compatibility testing of blood and blood components.

(2) Blood and blood components not suitable for use or distribution.

Subpart D—Equipment

§ 606.60 Equipment.

(a) Equipment used in the collection, processing, compatibility testing, storage and distribution of blood and blood components shall be maintained in a clean and orderly manner and located so as to facilitate cleaning and maintenance. The equipment shall be observed, standardized and calibrated on a regularly scheduled basis as prescribed in the Standard Operating Procedures Manual and shall perform in the manner for which it was designed so as to assure compliance with the official requirements prescribed in this chapter for blood and blood products.

(b) Equipment that shall be observed, standardized and calibrated with at least the following frequency, include but are not limited to:

Equipment	Performance check	Frequency	Frequency of calibration
Temperature recorder	Compare against thermometer	Daily	As necessary.
Refrigerated centrifuge	Observe speed and temperature	Each day of use	Do.
Hematocrit centrifuge	.....	.....	Standardize before initial use, after repairs or adjustments, and annually. Timer every 3 mo.
General lab centrifuge	.....	.....	Tachometer every 6 mo.
Automated blood-typing machine.	Observe controls for correct results	Each day of use.	
Hemoglobinometer	Standardize against cyanmethemoglobin standard.	.....do	
Refractometer	Standardize against distilled water	.....do	
Blood container scale	Standardize against container of known weight.	.....do	As necessary.
Water bath	Observe temperature	.....do	Do.
Rh view box	.....do	.....do	Do.
Autoclave	.....do	Each time of use	Do.
Serologic rotators	Observe controls for correct results	Each day of use	Speed as necessary.
Laboratory thermometers	.....	.....	Before initial use.
Electronic thermometers	.....	.....	Monthly.
Vacuum blood agitator	Observe weight of the first container of blood filled for correct results.	Each day of use	Standardize with container of known mass or volume before initial use, and after repairs or adjustments.

(c) Equipment employed in the sterilization of materials used in blood collection or for disposition of contaminated products shall be designed, maintained and utilized to ensure the destruction of contaminating microorganisms. The effectiveness of the sterilization procedure shall be no less than that achieved by an attained temperature of 121.5 °C (251 °F) maintained for 20 minutes by saturated steam or by an attained temperature of 170 °C (338 °F) maintained for 2 hours with dry heat.

[40 FR 53532, Nov. 18, 1975; 40 FR 55849, Dec. 2, 1975, as amended at 45 FR 9261, Feb. 12, 1980; 57 FR 11263, Apr. 2, 1992; 57 FR 12862, Apr. 13, 1992]

§ 606.65 Supplies and reagents.

All supplies and reagents used in the collection, processing, compatibility testing, storage and distribution of blood and blood components shall be stored in a safe, sanitary and orderly manner.

(a) All surfaces coming in contact with blood and blood components intended for transfusion shall be sterile, pyrogen-free, and shall not interact with the product in such a manner as to have an adverse effect upon the safety, purity, potency or effectiveness of the product. All final containers and closures for blood and blood components not intended for transfusion shall be clean and free of surface solids and other contaminants.

(b) Each blood collecting container and its satellite container(s), if any, shall be examined visually for damage or evidence of contamination prior to its use and immediately after filling. Such examination shall include inspection for breakage of seals, when indicated, and abnormal discoloration. Where any defect is observed, the container shall not be used, or, if detected after filling, shall be properly discarded.

(c) Representative samples of each lot of the following reagents or solutions shall be tested on a regularly scheduled basis by methods described in the Standard Operating Procedures Manual to determine their capacity to perform as required:

Reagent or solution	Frequency of testing
Anti-human globulin	Each day of use.
Blood grouping reagents	Do.
Lectins	Do.
Antibody screening and reverse grouping cells.	Do.
Hepatitis test reagents	Each run.
Syphilis serology reagents	Do.
Enzymes	Each day of use.

(d) Supplies and reagents that do not bear an expiration date shall be stored in such a manner that the oldest is used first.

(e) Supplies and reagents shall be used in a manner consistent with instructions provided by the manufacturer.

(f) Items that are required to be sterile and come into contact with blood should be disposable whenever possible.

[40 FR 53532, Nov. 18, 1975, as amended at 59 FR 23636, May 6, 1994]

Subpart E [Reserved]

Subpart F—Production and Process Controls

§ 606.100 Standard operating procedures.

(a) In all instances, except clinical investigations, standard operating procedures shall comply with published additional standards in part 640 of this chapter for the products being processed; except that, references in part 640 relating to licenses, licensed establishments and submission of material or data to or approval by the Director, Center for Biologics Evaluation and Research, are not applicable to establishments not subject to licensure under section 351 of the Public Health Service Act.

(b) Written standard operating procedures shall be maintained and shall include all steps to be followed in the collection, processing, compatibility testing, storage and distribution of blood and blood components for homologous transfusion, autologous transfusion and further manufacturing purposes. Such procedures shall be available to the personnel for use in the areas where the procedures are performed, unless this is impractical. The written standard operating procedures shall include, but are not limited to,

descriptions of the following, when applicable:

(1) Criteria used to determine donor suitability, including acceptable medical history criteria.

(2) Methods of performing donor qualifying tests and measurements, including minimum and maximum values for a test or procedure when a factor in determining acceptability.

(3) Solutions and methods used to prepare the site of phlebotomy to give maximum assurance of a sterile container of blood.

(4) Method of accurately relating the product(s) to the donor.

(5) Blood collection procedure, including in-process precautions taken to measure accurately the quantity of blood removed from the donor.

(6) Methods of component preparation, including any time restrictions for specific steps in processing.

(7) All tests and repeat tests performed on blood and blood components during processing, including testing for hepatitis B surface antigen as prescribed in §610.40 of this chapter.

(8) Pretransfusion testing, where applicable, including precautions to be taken to identify accurately the recipient blood samples and crossmatched donor units.

(9) Procedures for investigating adverse donor and recipient reactions.

(10) Storage temperatures and methods of controlling storage temperatures for all blood products and reagents as prescribed in §§600.15 and 610.53 of this chapter.

(11) Length of expiration dates, if any, assigned for all final products as prescribed in §610.53 of this chapter.

(12) Criteria for determining whether returned blood is suitable for reissue.

(13) Procedures used for relating a unit of blood or blood component from the donor to its final disposition.

(14) Quality control procedures for supplies and reagents employed in blood collection, processing and pretransfusion testing.

(15) Schedules and procedures for equipment maintenance and calibration.

(16) Labeling procedures, including safeguards to avoid labeling mixups.

(17) Procedures of plasmapheresis, plateletpheresis, and leukapheresis, if performed, including precautions to be taken to ensure reinfusion of a donor's own cells.

(18) Procedure for preparing recovered (salvaged) plasma, if performed, including details of separation, pooling, labeling, storage and distribution.

(19) Procedures in accordance with §610.46 of this chapter to look at prior donations of Whole Blood, blood components, Source Plasma and Source Leukocytes from a donor who has donated blood and subsequently tests repeatedly reactive for antibody to human immunodeficiency virus (HIV) or otherwise is determined to be unsuitable when tested in accordance with §610.45 of this chapter. Procedures to quarantine in-house Whole Blood, blood components, Source Plasma and Source Leukocytes intended for further manufacture into injectable products that were obtained from such donors; procedures to notify consignees regarding the need to quarantine such products; procedures to determine the suitability for release of such products from quarantine; procedures to notify consignees of Whole Blood, blood components, Source Plasma and Source Leukocytes from such donors of the results of the antibody testing of such donors; and procedures in accordance with §610.47 of this chapter to notify attending physicians so that transfusion recipients are informed that they may have received Whole Blood and, blood components at increased risk for transmitting human immunodeficiency virus.

(c) All records pertinent to the lot or unit maintained pursuant to these regulations shall be reviewed before the release or distribution of a lot or unit of final product. The review or portions of the review may be performed at appropriate periods during or after blood collecting, processing, compatibility testing and storing. A thorough investigation, including the conclusions and followup, of any unexplained discrepancy or the failure of a lot or unit to meet any of its specifications shall be made and recorded.

(d) In addition to the requirements of this subpart and in conformity with this section, any facility may utilize current standard operating procedures such as the manuals of the following

organizations, as long as such specific procedures are consistent with, and at least as stringent as, the requirements contained in this part.

(1) American Association of Blood Banks.

(2) American National Red Cross.

(3) Other organizations or individual blood banks, subject to approval by the Director, Center for Biologics Evaluation and Research.

[40 FR 53532, Nov. 18, 1975, as amended at 49 FR 23833, June 8, 1984; 55 FR 11013, Mar. 26, 1990; 61 FR 47422, Sept. 9, 1996]

§ 606.110 Plateletpheresis, leukapheresis, and plasmapheresis.

(a) The use of plateletpheresis and leukapheresis procedures to obtain a product for a specific recipient may be at variance with the additional standards for specific products prescribed in this part provided that: (1) A physician has determined that the recipient must be transfused with the leukocytes or platelets from a specific donor, and (2) the procedure is performed under the supervision of a qualified licensed physician who is aware of the health status of the donor, and the physician has certified in writing that the donor's health permits plateletpheresis or leukapheresis.

(b) Plasmapheresis of donors who do not meet the donor requirements of §§ 640.63, 640.64 and 640.65 of this chapter for the collection of plasma containing rare antibodies shall be permitted only with the prior approval of the Director, Center for Biologics Evaluation and Research.

[40 FR 53532, Nov. 18, 1975, as amended at 49 FR 23833, June 8, 1984; 55 FR 11013, Mar. 26, 1990]

Subpart G—Finished Product Control

§ 606.120 Labeling, general requirements.

(a) Labeling operations shall be separated physically or spatially from other operations in a manner adequate to prevent mixups.

(b) The labeling operation shall include the following labeling controls:

(1) Labels shall be held upon receipt, pending review and proofing against an approved final copy, to ensure accuracy regarding identity, content, and conformity with the approved copy.

(2) Each type of label representing different products shall be stored and maintained in a manner to prevent mixups, and stocks of obsolete labels shall be destroyed.

(3) All necessary checks in labeling procedures shall be utilized to prevent errors in translating test results to container labels.

(c) All labeling shall be clear and legible.

[50 FR 35469, Aug. 30, 1985]

§ 606.121 Container label.

(a) The container label requirements are designed to facilitate the use of a uniform container label for blood and blood components (except Source Plasma) by all blood establishments. Single copies of an FDA guideline entitled ''Guideline for the Uniform Labeling of Blood and Blood Components'' are available upon request (under Docket No. 80N–0120) from the Dockets Management Branch (HFA–305), Food and Drug Administration, Rm. 1–23, 12420 Parklawn Dr., Rockville, MD 20857 (copies of the guideline are available also from the American Blood Commission, 1901 North Ft. Myer Drive, Suite 300, Arlington, VA 22209).

(b) The label provided by the collecting facility and the initial processing facility shall not be removed, altered, or obscured, except that the label may be altered to indicate the proper name and other information required to identify accurately the contents of a container after blood components have been prepared.

(c) The container label shall include the following information, as well as other specialized information as required in this section for specific products:

(1) The proper name of the product in a prominent position, and modifier(s), if appropriate.

(2) The name, address, registration number, and, if a licensed product, the license number of each manufacturer.

(3) The donor, pool, or lot number relating the unit to the donor.

(4) The expiration date, including the day, month, and year, and, if the dating period for the product is 72 hours or less, the hour of expiration.

(5) If the product is intended for transfusion, the appropriate donor classification statement, i.e., ''paid donor'' or ''volunteer donor'', in no less prominence than the proper name of the product.

(i) A paid donor is a person who receives monetary payment for a blood donation.

(ii) A volunteer donor is a person who does not receive monetary payment for a blood donation.

(iii) Benefits, such as time off from work, membership in blood assurance programs, and cancellation of nonreplacement fees that are not readily convertible to cash, do not constitute monetary payment within the meaning of this paragraph.

(6) For Whole Blood, Plasma, Platelets, and partial units of Red Blood Cells, the volume of the product, accurate to within ±10 percent; or optionally for Platelets, the volume range within reasonable limits.

(7) The recommended storage temperature (in degrees Celsius).

(8) If the product is intended for transfusion, the statements:

(i) ''Caution: Federal law prohibits dispensing without prescription.''

(ii) ''See circular of information for indications, contraindications, cautions, and methods of infusion.''

(iii) ''Properly identify intended recipient.''

(9) The statement: ''This product may transmit infectious agents.''

(10) Where applicable, the name and volume of source material.

(11) The statement: ''Caution: For Manufacturing Use Only'', when applicable.

(12) If the product is intended for transfusion, the ABO and Rh groups of the donor shall be designated conspicuously. For Cryoprecipitated AHF, the Rh group may be omitted. The Rh group shall be designated as follows:

(i) If the test using Anti-D Blood Grouping Reagent is positive, the product shall be labeled: ''Rh positive.''

(ii) If the test using Anti-D Blood Grouping Reagent is negative but the test for D^u is positive, the product shall be labeled: ''Rh positive.''

(iii) If the test using Anti-D Blood Grouping Reagent is negative and the test for D^u is negative, the product shall be labeled: ''Rh negative.''

(13) The container label may bear encoded information in the form of machine-readable symbols approved for use by the Director, Center for Biologics Evaluation and Research (HFB–1).

(d) Except for recovered plasma intended for manufacturing use or as otherwise approved by the Director, Center for Biologics Evaluation and Research (HFB–1), the paper of the container label shall be white and print shall be solid black, with the following additional exceptions:

(1) The Rh blood group shall be printed as follows:

(i) Rh positive: Use black print on white background.

(ii) Rh negative: Use white print on black background.

(2) The proper name of the product, any appropriate modifier(s), the donor classification statement, and the statement ''properly identify intended recipient'' shall be printed in solid red.

(3) The following color scheme may be used optionally for differentiating ABO Blood groups:

Blood group	Color of label paper
O	Blue
A	Yellow
B	Pink
AB	White

(4) Ink colors used for the optional color coding system described in paragraph (d)(3) of this section shall be a visual match to specific color samples designated by the Director, Center for Biologics Evaluation and Research (HFB–1).

(5) Special labels, such as those described in paragraphs (h) and (i) of this section, may be color coded using the colors recommended in the guideline (see paragraph (a) of this section), or colors otherwise approved for use by the Director, Center for Biologics Evaluation and Research (HFB–1).

(e) Container label requirements for particular products or groups of products.

(1) Whole Blood labels shall include:

(i) The volume of anticoagulant.

(ii) The name of the applicable anticoagulant immediately preceding and of no less prominence than the proper name and expressd as follows: (*a*) ACD, (*b*) CPD, (*c*) Heparin, (*d*) CPDA–1, (*e*) CP2D, or by other nomenclature approved for use by the Director, Office of Biologics Research and Review (HFN–800), Center for Drugs and Biologics.

(iii) If tests for unexpected antibodies are positive, blood intended for transfusion shall be labeled: ''Contains (*name of antibody*).''

(2) Except for frozen, deglycerolized, or washed Red Blood Cell products, red blood cell labels shall include:

(i) The volume and kind of Whole Blood, including the type of anticoagulant, from which the product was prepared.

(ii) If tests for unexpected antibodies are positive and the product is intended for transfusion, the statement: ''Contains (*name of antibody*).''

(3) Labels for products with a dating period of 72 hours or less, including any product prepared in a system that may compromise sterility, shall bear the hour of expiration.

(4) If tests for unexpected antibodies are positive, Plasma intended for transfusion shall be labeled: ''Contains (*name of antibody*).''

(5) Recovered plasma labels shall include:

(i) In lieu of an expiration date, the date of collection of the oldest material in the container.

(ii) The statement: ''Caution: For Manufacturing Use Only''; or ''Caution: For Use in Manufacturing Noninjectable Products Only'', as applicable.

(iii) For recovered plasma not meeting the requirements for manufacture into licensable products, the statement: ''Not for Use in Products Subject to License Under Section 351 of the Public Health Service Act.''

(f) Blood and blood components determined to be unsuitable for transfusion shall be prominently labeled: ''NOT FOR TRANSFUSION'', and the label shall state the reason the unit is considered unsuitable. The provision does not apply to recovered plasma labeled according to paragraph (e)(5) of this section.

(g) As required under §610.40 of this chapter, labels for blood and blood components that are reactive for Hepatitis B Surface Antigen, but that are intended for further manufacturing, shall state conspicuously that the material is reactive when tested for hepatitis B surface antigen and may transmit viral hepatitis or, as applicable, that blood was collected from a donor known to be reactive for hepatitis B surface antigen and is presumed to be infectious, although confirmatory hepatitis testing has not been done.

(h) The following additional information shall appear on the label for blood or blood components shipped in an emergency, prior to completion of required tests, in accordance with §640.2(f) of this chapter:

(1) The statement: ''FOR EMERGENCY USE ONLY BY _____.''

(2) Results of any tests prescribed under §§610.40, 610.45, and 640.5 (a), (b), or (c) of this chapter completed before shipment.

(3) Indication of any tests prescribed under §§610.40, 610.45, and 640.5 (a), (b), or (c) of this chapter and not completed before shipment.

(i) The following additional information shall appear on the label for Whole Blood or Red Blood Cells intended for autologous infusion:

(1) Information adequately identifying the patient, e.g., name, blood group, hospital, and identification number.

(2) Date of donation.

(3) The statement: ''FOR AUTOLOGOUS USE ONLY.''

(4) In place of the blood group label, each container of blood intended for autologous use and obtained from a donor who fails to meet any of the donor suitability requirements under §640.3 of this chapter or who is reactive in the hepatitis tests prescribed under §610.40 of this chapter shall be prominently and permanently labeled: ''FOR AUTOLOGOUS USE ONLY.''

(5) Units of blood originally intended for autologous use, except those labeled as prescribed under paragraph (i)(4) of this section, may be issued for homologous transfusion provided the container label complies with all applicable provisions of paragraphs (b) through (e) of this section. In such

case, the special label required under paragraph (i) (1), (2), and (3) of this section shall be removed or otherwise obscured.

(j) A tie-tag attached to the container may be used for providing the information required by paragraph (e)(1)(iii), (2)(ii), and (4), (h), or (i)(1), (2), and (3) of this section.

[50 FR 35469, Aug. 30, 1985, as amended at 53 FR 116, Jan. 5, 1988; 55 FR 11014, Mar. 26, 1990; 57 FR 10814, Mar. 31, 1992; 59 FR 23636, May 6, 1994]

EFFECTIVE DATE NOTE: The information collection requirements contained in § 606.121 will not become effective until OMB approval has been obtained. FDA will publish a notice of OMB approval in the FEDERAL REGISTER.

§ 606.122 Instruction circular.

An instruction circular shall be available for distribution if the product is intended for transfusion. The instruction circular shall provide adequate directions for use, including the following information:

(a) Instructions to mix the product before use.

(b) Instructions to use a filter in the administration equipment.

(c) The statement ''Do Not Add Medications'' or an explanation concerning allowable additives.

(d) A description of the product, its source, and preparation, including the name and proportion of the anticoagulant used in collecting the Whole Blood from each product is prepared.

(e) Statements that the product was prepared from blood that was negative when tested for antibody to Human Immunodeficiency Virus (HIV) and nonreactive for hepatitis B surface antigen by FDA required tests and nonreactive when tested for syphilis by a serologic test for syphilis (STS).

(f) The statements: ''Warning. The risk of transmitting hepatitis is present. Careful donor selection and available laboratory tests do not eliminate the hazard.''

(g) The names of cryoprotective agents and other additives that may still be present in the product.

(h) The names and results of all tests performed when necessary for safe and effective use.

(i) The use of the product, indications, contradications, side effects and hazards, dosage and administration recommendations.

(j) [Reserved]

(k) For Red Blood Cells, the instruction circular shall contain:

(1) Instructions to administer a suitable plasma volume expander if Red Blood Cells are substituted when Whole Blood is the indicated product.

(2) A warning not to add Lactated Ringer's Injection U.S.P. solution to Red Blood Cell products.

(l) For Platelets, the instruction circular shall contain:

(1) The approximate volume of plasma from which a sample unit of Platelets is prepared.

(2) Instructions to begin administration as soon as possible, but not more than 4 hours after entering the container.

(m) For Plasma, the instruction circular shall contain:

(1) A warning against further processing of the frozen product if there is evidence of breakage or thawing.

(2) Instructions to thaw the frozen product at a temperature between 30 and 37 °C.

(3) When applicable, instructions to begin administration of the product within 6 hours after thawing.

(4) Instructions to administer to ABO-group-compatible recipients.

(5) A statement that this product has the same hepatitis risk as Whole Blood; other plasma volume expanders without this risk are available for treating hypovolemia.

(n) For Cryoprecipitated AHF, the instruction circular shall contain:

(1) A statement that the average potency is 80 or more International Units of antihemophilic factor.

(2) The statement: ''Usually contains at least 150 milligrams of fibrinogen''; or, alternatively, the average fibrinogen level determined by assay of representative units.

(3) A warning against further processing of the product if there is evidence of breakage or thawing.

(4) Instructions to thaw the product for no more than 15 minutes at a temperature of 37 °C.

(5) Instructions to store at room temperature after thawing and to begin administration as soon as possible but no more than 4 hours after entering the container or after pooling and within 6 hours after thawing.

(6) A statement that 0.9 percent Sodium Chloride Injection U.S.P. is the preferred diluent.

(7) Adequate instructions for pooling to ensure complete removal of all concentrated material from each container.

(8) The statement: ''Good patient management requires monitoring treatment responses to Cryoprecipitated AHF transfusions with periodic plasma factor VIII or fibrinogen assays in hemophilia A and hypofibrinogenemic recipients, respectively.''

[50 FR 35470, Aug. 30, 1985, as amended at 53 FR 116, Jan. 5, 1988]

EFFECTIVE DATE NOTE: The information collection requirements contained in §606.122 will not become effective until OMB approval has been obtained. FDA will publish a notice of OMB approval in the FEDERAL REGISTER.

Subpart H—Laboratory Controls

§ 606.140 Laboratory controls.

Laboratory control procedures shall include:

(a) The establishment of scientifically sound and appropriate specifications, standards and test procedures to assure that blood and blood components are safe, pure, potent and effective.

(b) Adequate provisions for monitoring the reliability, accuracy, precision and performance of laboratory test procedures and instruments.

(c) Adequate identification and handling of all test samples so that they are accurately related to the specific unit of product being tested, or to its donor, or to the specific recipient, where applicable.

§ 606.151 Compatibility testing.

Standard operating procedures for compatibility testing shall include the following:

(a) A method of collecting and identifying the blood samples of recipients to ensure positive identification.

(b) The use of fresh recipient serum samples less than 48 hours old for all pretransfusion testing.

(c) The testing of the donor's cells with the recipient's serum (major crossmatch) by a method that will demonstrate agglutinating, coating and hemolytic antibodies, which shall include the antiglobulin method.

(d) A provision that, if the unit of donor's blood has not been screened by a method that will demonstrate agglutinating, coating and hemolytic antibodies, the recipient's cells shall be tested with the donor's serum (minor crossmatch) by a method that will so demonstrate.

(e) Procedures to expedite transfusions in life-threatening emergencies. Records of all such incidents shall be maintained, including complete documentation justifying the emergency action, which shall be signed by the physician requesting the procedure.

Subpart I—Records and Reports

§ 606.160 Records.

(a)(1) Records shall be maintained concurrently with the performance of each significant step in the collection, processing, compatibility testing, storage and distribution of each unit of blood and blood components so that all steps can be clearly traced. All records shall be legible and indelible, and shall identify the person performing the work, include dates of the various entries, show test results as well as the interpretation of the results, show the expiration date assigned to specific products, and be as detailed as necessary to provide a complete history of the work performed.

(2) Appropriate records shall be available from which to determine lot numbers of supplies and reagents used for specific lots or units of the final product.

(b) Records shall be maintained that include, but are not limited to, the following when applicable:

(1) Donor records:

(i) Donor selection, including medical interview and examination and where applicable, informed consent.

(ii) Permanent and temporary deferrals for health reasons including reason(s) for deferral.

(iii) Donor adverse reaction complaints and reports, including results of all investigations and followup.

(iv) Therapeutic bleedings, including signed requests from attending physicians, the donor's disease and disposition of units.

(v) Immunization, including informed consent, identification of the antigen, dosage and route of administration.

(vi) Blood collection, including identification of the phlebotomist.

(vii) Records to relate the donor with the unit number of each previous donation from that donor.

(viii) Records of quarantine, notification, testing, and disposition performed pursuant to §§ 610.46 and 610.47 of this chapter.

(2) Processing records:

(i) Blood processing, including results and interpretation of all tests and retests.

(ii) Component preparation, including all relevant dates and times.

(iii) Separation and pooling of recovered plasma.

(iv) Centrifugation and pooling of source plasma.

(v) Labeling, including initials of person(s) responsible.

(3) Storage and distribution records:

(i) Distribution and disposition, as appropriate, of blood and blood products.

(ii) Visual inspection of whole blood and red blood cells during storage and immediately before distribution.

(iii) Storage temperature, including initialed temperature recorder charts.

(iv) Reissue, including records of proper temperature maintenance.

(v) Emergency release of blood, including signature of requesting physician obtained before or after release.

(4) Compatibility test records:

(i) Results of all compatibility tests, including crossmatching, testing of patient samples, antibody screening and identification.

(ii) Results of confirmatory testing.

(5) Quality control records:

(i) Calibration and standardization of equipment.

(ii) Performance checks of equipment and reagents.

(iii) Periodic check on sterile technique.

(iv) Periodic tests of capacity of shipping containers to maintain proper temperature in transit.

(v) Proficiency test results.

(6) Transfusion reaction reports and complaints, including records of investigations and followup.

(7) General records:

(i) Sterilization of supplies and reagents prepared within the facility, including date, time interval, temperature and mode.

(ii) Responsible personnel.

(iii) Errors and accidents.

(iv) Maintenance records for equipment and general physical plant.

(v) Supplies and reagents, including name of manufacturer or supplier, lot numbers, expiration date and date of receipt.

(vi) Disposition of rejected supplies and reagents used in the collection, processing and compatibility testing of blood and blood components.

(c) A donor number shall be assigned to each accepted donor, which relates the unit of blood collected to that donor, to his medical record, to any component or blood product from that donor's unit of blood, and to all records describing the history and ultimate disposition of these products.

(d) Records shall be retained for such interval beyond the expiration date for the blood or blood component as necessary to facilitate the reporting of any unfavorable clinical reactions. The retention period shall be no less than 5 years after the records of processing have been completed or 6 months after the latest expiration date for the individual product, whichever is a later date. When there is no expiration date, records shall be retained indefinitely.

(e) A record shall be available from which unsuitable donors may be identified so that products from such individuals will not be distributed.

[40 FR 53532, Nov. 18, 1975, as amended at 61 FR 47422, Sept. 9, 1996]

§ 606.165 Distribution and receipt; procedures and records.

(a) Distribution and receipt procedures shall include a system by which the distribution or receipt of each unit

can be readily determined to facilitate its recall, if necessary.

(b) Distribution records shall contain information to readily facilitate the identification of the name and address of the consignee, the date and quantity delivered, the lot number of the unit(s), the date of expiration or the date of collection, whichever is applicable, or for crossmatched blood and blood components, the name of the recipient.

(c) Receipt records shall contain the name and address of the collecting facility, date received, donor or lot number assigned by the collecting facility and the date of expiration or the date of collection, whichever is applicable.

§ 606.170 Adverse reaction file.

(a) Records shall be maintained of any reports of complaints of adverse reactions regarding each unit of blood or blood product arising as a result of blood collection or transfusion. A thorough investigation of each reported adverse reaction shall be made. A written report of the investigation of adverse reactions, including conclusions and followup, shall be prepared and maintained as part of the record for that lot or unit of final product by the collecting or transfusing facility. When it is determined that the product was at fault in causing a transfusion reaction, copies of all such written reports shall be forwarded to and maintained by the manufacturer or collecting facility.

(b) When a complication of blood collection or transfusion is confirmed to be fatal, the Director, Office of Compliance, Center for Biologics Evaluation and Research, shall be notified by telephone or telegraph as soon as possible; a written report of the investigation shall be submitted to the Director, Office of Compliance, Center for Biologics Evaluation and Research, within 7 days after the fatality by the collecting facility in the event of a donor reaction, or by the facility that performed the compatibility tests in the event of a transfusion reaction.

(Information collection requirements approved by the Office of Management and Budget under control number 0910–0116)

[40 FR 53532, Nov. 18, 1975, as amended at 49 FR 23833, June 8, 1984; 50 FR 35471, Aug. 30, 1985; 55 FR 11014, Mar. 26, 1990]

PART 607—ESTABLISHMENT REGISTRATION AND PRODUCT LISTING FOR MANUFACTURERS OF HUMAN BLOOD AND BLOOD PRODUCTS

Subpart A—General Provisions

Sec.

Subpart B—Procedures for Domestic Blood Product Establishments

Subpart C—Procedures for Foreign Blood Product Establishments

Subpart D—Exemptions

AUTHORITY: 21 U.S.C. 321, 331, 351, 352, 355, 360, 371, 374; 42 U.S.C. 216, 262.

SOURCE: 40 FR 52788, Nov. 12, 1975, unless otherwise noted.

Subpart A—General Provisions

§ 607.3 Definitions.

(a) The term *act* means the Federal Food, Drug, and Cosmetic Act approved June 25, 1938 (52 Stat. 1040 et seq., as amended, 21 U.S.C. 301–392).

(b) *Blood and blood product* means a drug which consists of human whole blood, plasma, or serum or any product derived from human whole blood, plasma or serum, hereinafter referred to as ''blood product.''

(c) *Establishment* means a place of business under one management at one general physical location. The term includes, among others, human blood and plasma donor centers, blood banks, transfusion services, other blood product manufacturers and independent laboratories that engage in quality control and testing for registered blood product establishments.

(d) *Manufacture* means the collection, preparation, processing or compatibility testing by chemical, physical, biological, or other procedures of any blood product which meets the definition of a drug as defined in section 201(g) of the act, and including manipulation, sampling, testing, or control procedures applied to the final product or to any part of the process. The term includes packaging, labeling, repackaging or otherwise changing the container, wrapper, or labeling of any blood product package in furtherance of the distribution of the blood product from the original place of manufacture to the person who makes final delivery or sale to the ultimate consumer.

(e) *Commercial distribution* means any distribution of a blood product except pursuant to the investigational use provisions of part 312 of this chapter, but does not include internal or interplant transfer of a bulk product substance between registered domestic establishments within the same parent, subsidiary, and/or affiliate company.

(f) *Any material change* includes but is not limited to any change in the name of the blood product, in the quantity or identity of the active ingredient(s) or in the quantity or identity of the inactive ingredient(s) where quantitative listing of all ingredients is required pursuant to § 607.31(a)(2) and any significant change in the labeling of a blood product. Changes that are not significant include changes in arrangement or printing or changes of an editorial nature.

(g) *Bulk product substance* means any substance that is represented for use in a blood product and when used in the manufacturing of a blood product becomes an active ingredient or a finished dosage form of such product.

(h) *Advertising* and *labeling* include the promotional material described in § 202.1(l) (1) and (2) of this chapter, respectively.

(i) The definitions and interpretations contained in sections 201 and 510 of the act shall be applicable to such terms when used in this part 607.

[40 FR 52788, Nov. 12, 1975, as amended at 55 FR 11014, Mar. 26, 1990]

§ 607.7 Establishment registration and product listing of blood banks and other firms manufacturing human blood and blood products.

(a) All owners or operators of establishments that engage in the manufacturing of blood products are required to register, pursuant to section 510 of the Federal Food, Drug, and Cosmetic Act. Registration and listing of blood products shall comply with this part. Registration does not permit any blood bank or similar establishment to ship blood products in interstate commerce.

(b) Forms for registration of an establishment are obtainable on request from the Center for Biologics Evaluation and Research (HFB–240), 8800 Rockville Pike, Bethesda, MD 20892 or at any of the Food and Drug Administration district offices.

(c) The completed form should be mailed to the Center for Biologics Evaluation and Research (HFB–240), 8800 Rockville Pike, Bethesda, MD 20892.

[40 FR 52788, Nov. 12, 1975, as amended at 49 FR 23833, June 8, 1984; 55 FR 11014, Mar. 26, 1990]

Subpart B—Procedures for Domestic Blood Product Establishments

§ 607.20 Who must register and submit a blood product list.

(a) Owners or operators of all establishments, not exempt under section 510(g) of the act or subpart D of this part 607, that engage in the manufacture of blood products are required to register and to submit a list of every blood product in commercial distribution (except that listing information

may be submitted by the parent, subsidiary, and/or affiliate company for all establishments when operations are conducted at more than one establishment and there exists joint ownership and control among all the establishments), whether or not the output of such blood product establishment or any particular blood product so listed enters interstate commerce.

(b) Preparatory to engaging in the manufacture of blood products, owners or operators of establishments who are submitting an establishment license application to manufacture blood products are required to register before the establishment license application is approved.

(c) No registration fee is required. Establishment registration and blood product listing do not constitute an admission or agreement or determination that a blood product is a ''drug'' within the meaning of section 201(g) of the act.

§ 607.21 Times for establishment registration and blood product listing.

The owner or operator of an establishment entering into an operation defined in § 607.3(d) shall register such establishment within 5 days after the beginning of such operation and submit a list of every blood product in commercial distribution at the time. If the owner or operator of the establishment has not previously entered into such operation (defined in § 607.3(d)) for which a license is required, registration shall follow within 5 days after the submission of an establishment and product license application in order to manufacture blood products. Owners or operators of all establishments so engaged shall register annually between November 15 and December 31 and shall update their blood product listing information every June and December.

§ 607.22 How and where to register establishments and list blood products.

(a) The first registration of an establishment shall be on Form FD–2830 (Blood Establishment Registration and Product Listing) obtainable on request from the Department of Health and Human Services, Food and Drug Administration, Center for Biologics Evaluation and Research (HFB–240), 8800 Rockville Pike, Bethesda, MD 20892, or from Food and Drug Administration district offices. Subsequent annual registration shall also be accomplished on Form FD–2830 which will be furnished by the Food and Drug Administration before November 15 of each year to establishments whose product registration for that year was validated pursuant to § 607.35. The completed form shall be mailed to the above address before December 31 of that year.

(b) The first list of blood products and subsequent June and December updatings shall be on Form FD–2830, obtainable upon request as described in paragraph (a) of this section. In lieu of Form FD–2830, tapes for computer input may be submitted if equivalent in all elements of information as specified in Form FD–2830. All formats proposed for such use will require initial review and approval by the Office of Compliance, Center for Biologics Evaluation and Research, Food and Drug Administration.

[40 FR 52788, Nov. 12, 1975, as amended at 49 FR 23833, June 8, 1984; 55 FR 11014, Mar. 26, 1990]

§ 607.25 Information required for establishment registration and blood product listing.

(a) Form FD–2830 (Blood Establishment Registration and Product Listing) requires furnishing or confirming registration information required by the act. This information includes the name and street address of the establishment, including post office ZIP code; all trade names used by the establishment; the kind of ownership or operation (that is, individually owned partnership, or corporation); and the name of the owner or operator of such establishment. The term ''name of the owner or operator'' shall include in the case of a partnership the name of each partner, and in the case of a corporation the name and title of each corporate officer and director and the name of the State of incorporation. The information required shall be given separately for each establishment, as defined in § 607.3(c).

(b) Form FD–2830 also requires furnishing blood product listing information required by the act as follows:

(1) A list of blood products, including bulk product substances as well as finished dosage forms, by established name as defined in section 502(e) of the act and by proprietary name, which are being manufactured for commercial distribution and which have not been included in any list previously submitted on Form FD–2830 (Blood Establishment Registration and Product Listing) or Form FD–2250 (National Drug Code Directory Input).

(2) For each blood product so listed which is subject to section 351 of the Public Health Service Act, the license number of the manufacturer issued by the Center for Biologics Evaluation and Research, Food and Drug Administration.

(3) For each blood product listed, the registration number of every blood product establishment within the parent company at which it is manufactured.

[40 FR 52788, Nov. 12, 1975, as amended at 49 FR 23833, June 8, 1984; 55 FR 11013, Mar. 26, 1990]

§ 607.26 Amendments to establishment registration.

Changes in individual ownership, corporate or partnership structure location or blood-product-handling activity, shall be submitted on Form FD–2830 (Blood Establishment Registration and Product Listing) as amendment to registration within 5 days of such changes. Changes in the names of officers and directors of the corporations do not require such amendment but must be shown at time of annual registration.

§ 607.30 Updating blood product listing information.

(a) After submission of the initial blood product listing information, every person who is required to list blood products pursuant to § 607.20 shall submit on Form FD–2830 (Blood Establishment Registration and Product Listing) during each subsequent June and December, or at the discretion of the registrant at the time the change occurs, the following information:

(1) A list of each blood product introduced by the registrant for commercial distribution which has not been included in any list previously submitted. All of the information required by § 607.25(b) shall be provided for each such blood product.

(2) A list of each blood product formerly listed pursuant to § 607.25(b) for which commercial distribution has been discontinued, including for each blood product so listed the identity by established name and proprietary name, and date of discontinuance. It is requested but not required that the reason for discontinuance of distribution be included with this information.

(3) A list of each blood product for which a notice of discontinuance was submitted pursuant to paragraph (a)(2) of this section and for which commercial distribution has been resumed, including for each blood product so listed the identity by established name as defined in section 502(e) of the act and by any proprietary name, the date of resumption, and any other information required by § 607.25(b) not previously submitted.

(4) Any material change in any information previously submitted.

(b) When no changes have occurred since the previously submitted list, no listing information is required.

§ 607.31 Additional blood product listing information.

(a) In addition to the information routinely required by §§ 607.25 and 607.30, the Commissioner may require submission of the following information by letter or by FEDERAL REGISTER notice:

(1) For a particular blood product so listed, upon request made by the Commissioner for good cause, a copy of all advertisements.

(2) For a particular blood product so listed, upon a finding by the Commissioner that it is necessary to carry out the purposes of the act, a quantitative listing of all ingredients.

(3) For each registrant, upon a finding by the Commissioner that it is necessary to carry out the purposes of the act, a list of each listed blood product containing a particular ingredient.

(b) It is requested but not required that information concerning the quantity of blood product distributed be submitted in conjunction with the annual registration in the format prescribed in a section of Form FD–2831 (Blood Establishment Resource Summary), for each blood product currently listed.

§ 607.35 Notification of registrant; blood product establishment registration number and NDC Labeler Code.

(a) The Commissioner will provide to the registrant a validated copy of Form FD–2830 (Blood Establishment Registration and Product Listing) as evidence of registration. This validated copy will be sent only to the location shown for the registering establishment. A permanent registration number will be assigned to each blood product establishment registered in accordance with these regulations.

(b) If a registered blood product establishment has not previously participated in the National Drug Code system, or in the National Health Related Items Code system, the National Drug Code (NDC) numbering system shall be used in assigning the first five numeric characters, otherwise known as the Labeler Code, of the 10-character NDC Code. The Labeler Code identifies the manufacturer.

(c) Although establishment registration and blood product listing are required as described in §607.20, validation of registration and the assignment of a NDC Labeler Code do not, in themselves, establish that the holder of the registration is legally qualified to deal in such products.

[40 FR 52788, Nov. 12, 1975, as amended at 49 FR 23833, June 8, 1984]

§ 607.37 Inspection of establishment registrations and blood product listings.

(a) A copy of the Form FD–2830 (Blood Establishment Registration and Product Listing) filed by the registrant will be available for inspection pursuant to section 510(f) of the act, at the Department of Health and Human Services, Food and Drug Administration, Office of Compliance, Center for Biologics Evaluation and Research (HFB–100), 8800 Rockville Pike, Bethesda, MD 20892. In addition, there will be available for inspection at each of the Food and Drug Administration district offices the same information for firms within the geographical area of such district office. Upon request and receipt of a self-addressed stamped envelope, verification of registration number, or location of a registered establishment will be provided. The following information submitted pursuant to the blood product listing requirements is illustrative of the type of information that will be available for public disclosure when it is compiled:

(1) A list of all blood products.

(2) A list of all blood products manufactured by each establishment.

(3) A list of blood products discontinued.

(4) All data or information that has already become a matter of public knowledge.

(b) Requests for information regarding blood establishment registrations and blood product listings should be directed to the Department of Health and Human Services, Food and Drug Administration, Office of Compliance, Center for Biologics Evaluation and Research (HFB–100), 8800 Rockville Pike, Bethesda, MD 20892.

[40 FR 52788, Nov. 12, 1975, as amended at 49 FR 23833, June 8, 1984; 55 FR 11014, Mar. 26, 1990]

§ 607.39 Misbranding by reference to establishment registration or to registration number.

Registration of an establishment or assignment of a registration number or assignment of a NDC number does not in any way denote approval of the firm or its products. Any representation that creates an impression of official approval because of establishment registration or possession of registration number or NDC number is misleading and constitutes misbranding.

Subpart C—Procedures for Foreign Blood Product Establishments

§ 607.40 Blood product listing requirements for foreign blood product establishments.

(a) Every foreign establishment shall comply with the blood product listing

requirements contained in Subpart B of this part, unless exempt under Subpart D of this part, whether or not it is also registered.

(b) No blood product may be imported from a foreign establishment into the United States except a blood product imported or offered for import pursuant to the investigational use provisions of part 312 of this chapter, unless it is first the subject of a blood product listing as required in Subpart B of this part. The blood product listing information shall be in the English language.

(c) Foreign establishments shall submit, as part of the blood product listing, the name and address of the establishment and the name of the individual responsible for submitting blood product listing information. Any changes in this information shall be reported to the Food and Drug Administration at the intervals specified for updating blood product listing information in §607.30(a).

[40 FR 52788, Nov. 12, 1975, as amended at 55 FR 11014, Mar. 26, 1990]

Subpart D—Exemptions

§607.65 Exemptions for blood product establishments.

The following classes of persons are exempt from registration and blood product listing in accordance with this part 607 under the provisions of section 510(g) (1), (2), and (3) of the act, or because the Commissioner has found, under section 510(g)(4), that such registration is not necessary for the protection of the public health.

(a) Pharmacies that are operating under applicable local laws regulating dispensing of prescription drugs and that are not manufacturing blood products for sale other than in the regular course of the practice of the profession of pharmacy including the business of dispensing and selling blood products at retail. The supplying by such pharmacies of blood products to a practitioner licensed to administer such blood products for his use in the course of his professional practice or to other pharmacies to meet temporary inventory shortages are not acts which require such pharmacies to register.

(b) Practitioners who are licensed by law to prescribe or administer drugs and who manufacture blood products solely for use in the course of their professional practice.

(c) Persons who manufacture blood products which are not for sale, rather, are solely for use in research, teaching, or analysis, including laboratory samples.

(d) Carriers, by reason of their receipt, carriage, holding, or delivery of blood products in the usual course of business as carriers.

(e) Persons who engage solely in the manufacture of in vitro diagnostic blood products and reagents not subject to licensing under section 351 of the Public Health Service Act (42 U.S.C. 262). This paragraph does not exempt such persons from registration and listing for medical devices required under part 807 of this chapter.

(f) Transfusion services which are a part of a facility approved for Medicare reimbursement and engaged in the compatibility testing and transfusion of blood and blood components, but which neither routinely collect nor process blood and blood components. The collection and processing of blood and blood components in an emergency situation as determined by a responsible person and documented in writing, therapeutic collection of blood or plasma, the preparation of recovered human plasma for further manufacturing use, or preparation of red blood cells for transfusion are not acts requiring such transfusion services to register.

(g) Clinical laboratories that are approved for Medicare reimbursement and are engaged in the testing of blood products in support of other registered blood establishments.

[40 FR 52788, Nov. 12, 1975, as amended at 43 FR 37997, Aug. 25, 1978; 45 FR 85729, Dec. 30, 1980; 49 FR 34449, Aug. 31, 1984]

PART 610—GENERAL BIOLOGICAL PRODUCTS STANDARDS

Subpart A—Release Requirements

Sec.

Subpart B—General Provisions

Subpart C—Standard Preparations and Limits of Potency

Subpart D—Mycoplasma

Subpart E—Hepatitis Requirements

Subpart F—Dating Period Limitations

Subpart G—Labeling Standards

AUTHORITY: 21 U.S.C. 321, 351, 352, 353, 355, 360, 371; 42 U.S.C. 216, 262, 263, 263a, 264.

SOURCE: 38 FR 32056, Nov. 20, 1973, unless otherwise noted.

CROSS REFERENCES: For U.S. Customs Service regulations relating to viruses, serums, and toxins, see 19 CFR 12.21—12.23. For U.S. Postal Service regulations relating to the admissibility to the United States mails see parts 124 and 125 of the Domestic Mail Manual, that is incorporated by reference in 39 CFR part 111.

Subpart A—Release Requirements

§ 610.1 Tests prior to release required for each lot.

No lot of any licensed product shall be released by the manufacturer prior to the completion of tests for conformity with standards applicable to such product. Each applicable test shall be made on each lot after completion of all processes of manufacture which may affect compliance with the standard to which the test applies. The results of all tests performed shall be considered in determining whether or not the test results meet the test objective, except that a test result may be disregarded when it is established that the test is invalid due to causes unrelated to the product.

§ 610.2 Requests for samples and protocols; official release.

(a) *General.* Samples of any lot of any licensed product, except for radioactive biological products, together with the protocols showing results of applicable tests, may at any time be required to be sent to the Director, Center for Biologics Evaluation and Research. Upon notification by the Director, Center for Biologics Evaluation and Research, a manufacturer shall not distribute a lot of a product until the lot is released by the Director, Center for Biologics Evaluation and Research: *Provided,* That the Director, Center for Biologics Evaluation and Research, shall not issue such notification except when deemed necessary for the safety, purity, or potency of the product.

(b) *Radioactive biological products.* Samples of any lot of a radioactive biological product, as defined in § 600.3(ee) of this chapter, together with the protocols showing results of applicable tests, may at any time be required to be sent to the Food and Drug Administration for official release. Upon notification by the Director, Center for Drug Evaluation and Research, a manufacturer shall not distribute a lot of a radioactive biological product until the lot is released by the Director, Center for Drug Evaluation and Research: *Provided,* That the Director, Center for Drug Evaluation and Research shall not issue such notification except when

deemed necessary for the safety, purity, or potency of the product.

(Information collection requirements approved by the Office of Management and Budget under control number 0910–0206)

[40 FR 31313, July 25, 1975, as amended by 49 FR 23834, June 8, 1984; 50 FR 10941, Mar. 19, 1985; 55 FR 11013 and 11014, Mar. 26, 1990]

Subpart B—General Provisions

§610.9 Equivalent methods and processes.

Modification of any particular test method or manufacturing process or the conditions under which it is conducted as required in this part or in the additional standards for specific biological products in parts 620 through 680 of this chapter shall be permitted only under the following conditions:

(a) The applicant presents evidence, in the form of a license application, or a supplement to the application submitted in accordance with §601.12(b) or (c), demonstrating that the modification will provide assurances of the safety, purity, potency, and effectiveness of the biological product equal to or greater than the assurances provided by the method or process specified in the general standards or additional standards for the biological product; and

(b) Approval of the modification is received in writing from the Director, Center for Biologics Evaluation and Research, Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852–1448.

[62 FR 39903, July 24, 1997]

§610.10 Potency.

Tests for potency shall consist of either in vitro or in vivo tests, or both, which have been specifically designed for each product so as to indicate its potency in a manner adequate to satisfy the interpretation of potency given by the definition in §600.3(s) of this chapter.

§610.11 General safety.

A general safety test for the detection of extraneous toxic contaminants shall be performed on biological products intended for administration to humans. The general safety test is required in addition to other specific tests prescribed in the additional standards for individual products in this subchapter, except that, the test need not be performed on those products listed in paragraph (g) of this section. The general safety test shall be performed as specified in this section, unless: Modification is prescribed in the additional standards for specific products, or variation is approved as a supplement to the product license under §610.9.

(a) *Product to be tested.* The general safety test shall be conducted upon a representative sample of the product in the final container from every final filling of each lot of the product. If any product is processed further after filling, such as by freeze-drying, sterilization, or heat treatment, the test shall be conducted upon a sample from each filling of each drying chamber run, sterilization chamber, or heat treatment bath.

(b) *Test animals.* Only overtly healthy guinea pigs weighing less than 400 grams each and mice weighing less than 22 grams each shall be used. The animals shall not have been used previously for any test purpose.

(c) *Procedure.* The duration of the general safety test shall be 7 days for both species, except that a longer period may be established for specific products in accordance with §610.9. Once the manufacturer has established a specific duration of the test period for a specific product, it cannot be varied subsequently, except, in accordance with §610.9. Each test animal shall be weighed and the individual weights recorded immediately prior to injection and on the last day of the test. Each animal shall be observed every working day. Any animal response including any which is not specific for or expected from the product and which may indicate a difference in its quality shall be recorded on the day such response is observed. The test product shall be administered as follows:

(1) *Liquid product or freeze-dried product which has been reconstituted as directed on the label.* Inject intraperitoneally 0.5 milliliter of the liquid product or the reconstituted product into each of at least two mice, and 5.0 milliliters of the liquid product

or the reconstituted product into each of at least two guinea pigs.

(2) *Freeze-dried product for which the volume of reconstitution is not indicated on the label.* The route of administration, test dose, and diluent shall be as approved by the Director, Center for Biologics Evaluation and Research, in accordance with § 610.9. Administer the test product as approved on at least two mice and at least two guinea pigs.

(3) *Nonliquid products other than freeze-dried product.* The route of administration, test dose, and diluent shall be as approved by the Director, Center for Biologics Evaluation and Research, in accordance with § 610.9. Dissolve or grind and suspend the product in the approved diluent. Administer the test product as approved on at least two mice and at least two guinea pigs.

(d) *Test requirements.* A safety test is satisfactory if all animals meet all of the following requirements:

(1) They survive the test period.

(2) They do not exhibit any response which is not specific for or expected from the product and which may indicate a difference in its quality.

(3) They weigh no less at the end of the test period than at the time of injection.

(e) *Repeat tests*—(1) *First repeat test.* If a filling fails to meet the requirements of paragraph (d) of this section in the initial test, a repeat test may be conducted on the species which failed the initial test, as prescribed in paragraph (c) of this section. The filling is satisfactory only if each retest animal meets the requirements prescribed in paragraph (d) of this section.

(2) *Second repeat test.* If a filling fails to meet the requirements of the first repeat test, a second repeat test may be conducted on the species which failed the test: *Provided,* That 50 percent of the total number of animals in that species has survived the initial and first repeat tests. The second repeat test shall be conducted as prescribed in paragraph (c) of this section, except that the number of animals shall be twice that used in the first repeat test. The filling is satisfactory only if each second repeat test animal meets the requirements prescribed in paragraph (d) of this section.

(f) [Reserved]

(g) *Exceptions.* The test prescribed in this section need not be performed for Whole Blood, Red Blood Cells, Cryoprecipitated AHF, Platelets, or Plasma.

[41 FR 10891, Mar. 15, 1976, as amended at 49 FR 15187, Apr. 18, 1984; 49 FR 23834, June 8, 1984; 50 FR 4133, Jan. 29, 1985; 51 FR 15607, Apr. 25, 1986; 55 FR 11013, Mar. 26, 1990; 59 FR 49351, Sept. 28, 1994]

§ 610.11a Inactivated influenza vaccine, general safety test.

For inactivated influenza vaccine, the general safety test shall be conducted in the manner indicated in § 610.11 of this chapter except that, with reference to guinea pigs, the test shall be satisfied if the product provides satisfactory results using either the subcutaneous or intraperitoneal injection of 5.0 milliliters of inactivated influenza vaccine into each guinea pig. The requirements for general safety for inactivated influenza vaccine shall not be considered to be satisfied unless each lot of influenza vaccine is assayed for endotoxin in comparison to a reference preparation provided by the Food and Drug Administration, and such lot is found to contain no more endotoxin than the reference preparation.

[39 FR 40016, Nov. 13, 1974]

§ 610.12 Sterility.

Except as provided in paragraphs (f) and (g) of this section, the sterility of each lot of each product shall be demonstrated by the performance of the tests prescribed in paragraphs (a) and (b) of this section for both bulk and final container material.

(a) *The test.* Bulk material shall be tested separately from final container material and material from each final container shall be tested in individual test vessels as follows:

(1) *Using Fluid Thioglycollate Medium*—(i) *Bulk and final container material.* The volume of product, as required by paragraph (d) of this section (hereinafter referred to also as the ''inoculum''), from samples of both bulk and final container material, shall be inoculated into test vessels of Fluid Thioglycollate Medium. The inoculum and medium shall be mixed

thoroughly and incubated at a temperature of 30 to 35 °C for a test period of no less than 14 days and examined visually for evidence of growth on the third, fourth, or fifth day, and on the seventh or eighth day, and on the last day of the test period. Results of each examination shall be recorded. If the inoculum renders the medium turbid so that the absence of growth cannot be determined reliably by visual examination, portions of this turbid medium in amounts of no less than 1.0 milliliter shall be transferred on the third, fourth, or fifth day of incubation, from each of the test vessels and inoculated into additional vessels of the medium. The material in the additional vessels shall be incubated at a temperature of 30 to 35 °C for no less than 14 days. Notwithstanding such transfer of material, examination of the original vessels shall be continued as prescribed above. The additional test vessels shall be examined visually for evidence of growth on the third, fourth, or fifth day of incubation, and on the seventh or eighth day, and on the last day of the incubation period. If growth appears, repeat tests may be performed as prescribed in paragraph (b) of this section and interpreted as specified in paragraph (c) of this section.

(ii) *Final container material containing a mercurial preservative.* In addition to the test prescribed in paragraph (a)(1)(i) of this section, final container material containing a mercurial preservative shall be tested using Fluid Thioglycollate Medium following the procedures prescribed in such subparagraph, except that the incubation shall be at a temperature of 20 to 25 °C.

(2) *Using Soybean-Casein Digest Medium.* Except for products containing a mercurial preservative, a test shall be made on final container material, following the procedures prescribed in paragraph (a)(1)(i) of this section, except that the medium shall be Soybean-Casein Digest Medium and the incubation shall be at a temperature of 20 to 25 °C.

(b) *Repeat tests.* If growth appears in any of the test media during testing of either bulk or final container material, the test may be repeated to rule out faulty test procedures as follows:

(1) *Repeat bulk test.* Only one repeat bulk test may be conducted. The volume of inoculum to be used for the repeat bulk test shall be as prescribed in paragraph (d)(1) of this section. The repeat test shall be performed using the procedure prescribed in paragraph (a)(1)(i) of this section.

(2) *First repeat final container test.* The number of test samples and the volumes of product used for the first repeat test shall be as prescribed in paragraph (d)(2) of this section. For products that do not contain a mercurial preservative, the repeat test shall be performed, using both Fluid Thioglycollate Medium and Soybean-Casein Digest Medium, following the procedures prescribed in paragraphs (a)(1)(i) and (a)(2), respectively, of this section. If the product contains a mercurial preservative, the repeat test shall be performed using Fluid Thioglycollate Medium and the procedures prescribed in paragraphs (a)(1) (i) and (ii) of this section.

(3) *Second repeat final container test.* If growth appears in any of the first repeat final container tests, all tests of the first repeat final container test shall be repeated, provided there was no evidence of growth in any test of the bulk material. The test samples used for the second repeat final container test shall be twice the number used for the first repeat final container test.

(c) *Interpretation of test results.* The results of all tests performed on a lot shall be considered in determining whether or not the lot meets the requirements for sterility, except that tests may be excluded when demonstrated by adequate controls to be invalid. The lot meets the test requirements if no growth appears in the tests prescribed in paragraph (a) of this section. If repeat tests are performed, the lot meets the test requirements if no growth appears in the tests prescribed in paragraph (b)(2) or (3) of this section, whichever is applicable.

(d) *Test samples and volumes*—(1) *Bulk.* Each sample for the bulk sterility test shall be representative of the bulk material and the volume tested shall be no less than 10 ml. (Note exceptions in paragraph (g) of this section.)

(2) *Final containers.* The sample used for each test medium or each incubation temperature of a test medium for the final container and first repeat final container test shall be no less than 20 final containers from each filling of each lot, selected to represent all stages of filling from the bulk vessel. If the amount of material in the final container is 1.0 milliliter or less, the entire contents shall be tested. If the amount of material in the final container is more than 1.0 milliliter, the volume tested shall be the largest single dose recommended by the manufacturer or 1.0 milliliter, whichever is larger, but no more than 10 milliliters of material or the entire contents from a single final container need be tested. If more than 2 filling machines, each with either single or multiple filling stations, are used for filling one lot, no less than 10 filled containers shall be tested from each filling machine for each test medium or each incubation temperature condition, but no more than 100 containers of each lot need be tested. The items tested shall be representative of each filling assembly and shall be selected to represent all stages of the filling operation. (Note exceptions in paragraph (g) of this section.)

(e) *Culture medium*—(1) *Formulae.* (i) The formula for Fluid Thioglycollate Medium is as follows:

FLUID THIOGLYCOLLATE MEDIUM

1-cystine	0.5 gm.
Sodium chloride	2.5 gm.
Dextrose ($C_6H_{12}O_6 \cdot H_2O$)	5.5 gm.
Granular agar (less than 15% moisture by weight).	0.75 gm.
Yeast extract (water-soluble)	5.0 gm.
Pancreatic digest of casein	15.0 gm.
Purified water	1,000.0 ml.
Sodium thioglycollate (or thioglycolic acid—0.3 ml).	0.5 gm.
Resazurin (0.10% solution, 1.0 ml. freshly prepared).	

pH after sterilization 7.1±0.2.

(ii) The formula for Soybean-Casein Digest Medium is as follows:

SOYBEAN-CASEIN DIGEST MEDIUM

Pancreatic Digest of Casein	17.0 gm.
Papaic Digest of Soybean Meal	3.0 gm.
Sodium Chloride	5.0 gm.
Dibasic Potassium Phosphate	2.5 gm.
Dextrose ($C_6H_{12}O_6 \cdot H_2O$)	2.5 gm.
Purified water	1,000.0 ml.

pH after sterilization 7.3±0.2.

(2) *Culture media requirements*—(i) *Definition of a lot of culture medium and test requirements.* A lot of culture medium is that quantity of uniform material identified as having been thoroughly mixed in a single vessel, dispensed into a group of vessels of the same composition and design, sterilized in a single autoclave run, and identified in a manner to distinguish one lot from another. Each lot of culture medium shall be tested for its growth-promoting qualities unless it meets the exception for dehydrated culture medium described in this subpart. The growth-promoting quality test shall be performed on the smallest sized vessel used in an autoclave run. When using a single batch of dehydrated culture medium, a manufacturer need not perform growth-promoting tests on each lot of prepared liquid medium, provided that a validation program exists for autoclaves used to sterilize the culture medium, and the manufacturer has received approval for this practice from the Director, Center for Biologics Evaluation and Research.

(ii) *Test organisms, strains, characteristics, identity, and verification.* Two or more strains of microorganisms that are exacting in their nutritive and aerobic/anaerobic requirements shall be used to test the growth-promoting qualities of each lot of test medium. When using Fluid Thioglycollate medium, both an aerobic and an anaerobic test microorganism shall be chosen. When using Soybean Casein Digest Medium, the yeast, *Candida albicans,* shall be one of the two test microorganisms chosen. Manufacturers shall choose the strains of microorganisms from the chart in this paragraph.

Medium	Test microorganisms	Incubation temperature
	Spore-formers	
Fluid Thioglycollate	1. *Bacillus subtilis* (ATCC No. 6633)	30 to 35 °C.
	2. *Clostridium sporogenes* (ATCC No. 11437)	Do.
	Non-spore-formers	

Medium	Test microorganisms	Incubation temperature
	3. *Candida albicans* (ATCC No. 10231)	Do.
	4. *Micrococcus luteus* (ATCC No. 9341)	Do.
	5. *Bacteroides vulgatus* (ATCC No. 8482)	Do.
	Spore-formers	
Soybean-Casein Digest	1. *Bacillus subtilis* (ATCC No. 6633)	20 to 25 °C.
	Non-spore-formers	
	2. *Candida albicans* (ATCC No. 10231)	Do.
	3. *Micrococcus luteus* (ATCC No. 9341)	Do.

ATCC strains of microorganisms described in this section are available from the American Type Culture Collection, 12301 Parklawn Dr., Rockville, MD 20852. Periodic tests shall be performed to verify the integrity of the test organisms in accordance with §610.18 (a) and (b). The results of these periodic tests shall be recorded and retained in accordance with §600.12(b) of this chapter.

(iii) *Storage and maintenance of cultures of test organisms.* Cultures of the test organisms used to determine the growth-promoting qualities of the medium shall be stored in a manner that will prevent cross contamination or loss of identity, at a temperatre and by a method that will retain the initial characteristics of the organisms and ensure freedom from contamination and deterioration. If the test organisms are stored in the freeze-dried state, or frozen, they shall be reconstituted or thawed, whichever is applicable, and plated periodically to verify the colony count of the suspension. If the test suspensions are stored in a state other than freeze-dried or frozen, they shall be plated, and a colony count shall be performed at the time of each growth-promoting quality test to assure that not more than 100 organisms are used per test vessel. The results of tests for verification of the colony count shall be recorded and retained in accordance with §600.12(b) of this chapter.

(iv) *Storage and condition of media.* A medium shall not be used if the extent of evaporation affects its fluidity, nor shall it be reused in a sterility test of the product. Fluid Thioglycollate Medium shall be stored in the dark at room temperature if the vessels are unsealed. Sealed vessels shall be stored at the manufacturer's specified storage temperature.

Fluid Thioglycollate Medium shall not be used if more than the upper one-third of the medium has acquired a pink color. The medium may be restored once by heating on a steam bath or in free-flowing steam until the pink color disappears. The design of the test vessel for Fluid Thioglycollate Medium shall provide favorable aerobic and anaerobic conditions for growth of the microorganisms throughout the test period. Soybean-Casein Digest Medium shall be stored in the dark at 20 to 25 °C. Unsealed vessels of either medium may be stored for more than 10 days at the proper temperature, provided they are tested monthly for growth-promotion and found to be satisfactory. Sealed vessels of either medium may be stored at the proper temperature for a period of time not to exceed 1 year, provided they are tested for growth-promotion every 3 months and found to be satisfactory. The results of such testing shall be recorded and retained in accordance with §600.12(b) of this chapter.

(v) *Criteria for a satisfactory growth-promoting quality test.* (*a*) One hundred or fewer organisms of each strain tested shall be used. The test is satisfactory if evidence of growth appears within 7 days in all vessels inoculated. If a lot of medium fails to support the growth of any test organism, or if the test results show that more than 100 organisms of a strain were used or are necessary to promote growth in the lot of medium being tested, or if the growth is not a pure culture of the test organism, a second test may be performed. If it fails the second test, the lot of medium shall be rejected.

(*b*) Inoculated Fluid Thioglycollate Medium shall be incubated at 30 to 35 °C for 7 days. If the test medium is to be used in determining the sterility of

a product containing a mercurial preservative, a second test shall be performed in accordance with paragraph (e)(2)(v)(*a*) of this section, except that the test shall be incubated at 20 to 25 °C for 7 days. Inoculated Soybean-Casein Digest Medium shall be incubated at 20 to 25 °C for 7 days. The sterility of each lot of medium shall be confirmed by the incubation of uninoculated control test vessels for 7 days at the temperature(s) for that particular medium. The lot of medium is satisfactory if no growth is observed in the control test vessels within the incubation period. The tests for growth-promoting qualities of culture media may be performed simultaneously with sterility testing of biological products, provided the sterility test is considered invalid if the test medium shows no growth response.

(vi) *Volume of culture medium.* The volume of each culture medium shall be determined for each bulk and final container sterility test required for each product. The ratio of the volume of inoculum to the volume of culture medium shall result in a dilution of the product that is not bacteriostatic or fungistatic, except for products to be tested by membrane filtration. The volume of inhibitors or neutralizers of preservatives added should be considered in determining the proper ratio of inoculum/medium. Vessels of the product-medium mixture(s) and control vessels of the medium shall be inoculated with dilutions of cultures of bacteria or fungi which are viable in the product being tested, and incubated at the appropriate temperature for no less than 7 days.

(f) *Membrane filtration.* Bulk and final container material or products containing oil products in water-insoluble ointments may be tested for sterility using the membrane filtration procedure set forth in the United States Pharmacopeia (23d Revision, 1995), section entitled ''Test Procedures Using Membrane Filtration,'' pp. 1689 to 1690, which is incorporated by reference in accordance with 5 U.S.C. 552(a) and 1 CFR part 51. Copies are available from the United States Pharmacopeial Convention, Inc., 12601 Twinbrook Pkwy., Rockville, MD 20852, or available for inspection at the Center for Drug Evaluation and Research's Division of Medical Library, 5600 Fishers Lane, rm. 11B–40, Rockville, MD, or at the Office of the Federal Register, 800 North Capitol St. NW., suite 700, Washington, DC, except that:

(1) The test samples shall conform with paragraph (d) of this section; and

(2) In addition, for products containing a mercurial preservative, the product shall be tested in a second test using Fluid Thioglycollate Medium incubated at 20 to 25 °C in lieu of the test in Soybean-Casein Digest Medium.

(g) *Exceptions.* Bulk and final container material shall be tested for sterility as described above in this section, except as follows:

(1) *Different sterility tests prescribed.* When different sterility tests are prescribed for a product in this subchapter.

(2) *Alternate incubation temperatures.* Two tests may be performed as prescribed in paragraph (a)(1)(i) of this section, one test using an incubation temperature of 18 to 22 °C, the other test using an incubation temperature of 30 to 37 °C, in lieu of performing one test using an incubation temperature of 30 to 35 °C, provided that growth-promoting quality tests have been performed at these temperatures.

(3) [Reserved]

(4) *Test precluded or not required.* (i) The tests prescribed in this section need not be performed for Whole Blood, Cryoprecipitated AHF, Platelets, Red Blood Cells, Plasma, Source Plasma, Smallpox Vaccine, Reagent Red Blood Cells, Anti-Human Globulin, or Blood Grouping Reagent.

(ii) Where a manufacturer submits data which the Director, Center for Biologics Evaluation and Research, finds adequate to establish that the mode of administration, the method of preparation, or the special nature of the product precludes or does not require a sterility test or that the sterility of the lot is not necessary to assure the safety, purity, and potency of the product, the Director may exempt a product from the sterility requirements of this section subject to any conditions necessary to assure the safety, purity, and potency of the product.

(5) *Number of final containers more than 20, less than 200.* If the number of

final containers in the filling is more than 20 or less than 200, the sample shall be no less than 10 percent of the containers.

(6) *Number of final containers—20 or less.* If the number of final containers in a filling is 20 or less, the sample shall be two final containers, or the sample need be no more than one final container, provided (i) the bulk material met the sterility test requirements and (ii) after filling, it is demonstrated by testing a simulated sample that all surfaces to which the product was exposed were free of contaminating microorganisms. The simulated sample shall be prepared by rinsing the filling equipment with sterile 1.0 percent peptone solution, pH 7.1±0.1, which shall be discharged into a final container by the same method used for filling the final containers with the product.

(7) *Samples—large volume of product in final containers.* For Albumin (Human) and Plasma Protein Fraction (Human), when the volume of product in the final container is 50 milliliters or more, the final containers selected as the test sample may contain less than the full volume of product in the final containers of the filling from which the sample is taken: *Provided,* That the containers and closures of the sample are identical with those used for the filling to which the test applies, and the sample represents all stages of that filling.

(8) *Diagnostic biological products not intended for injection.* For diagnostic biological products not intended for injection, (i) only the Fluid Thioglycollate Medium test incubated at 30 to 35 °C is required, (ii) the volume of material for the bulk test shall be no less than 2.0 milliliters, and (iii) the sample for the final container test shall be no less than three final containers if the total number filled is 100 or less, and, if greater, one additional container for each additional 50 containers or fraction thereof, but the sample need be no more than 10 containers.

(9) *Immune globulin preparations.* For immune globulin preparations, the test samples from the bulk material and from each final container need be no more than 2.0 ml.

(h) *Records.* The records related to the testing requirements of this section shall be prepared and maintained as required by §§ 211.167 and 211.194 of this chapter.

(Information collection requirements approved by the Office of Management and Budget under control number 0910–0139)

[38 FR 32056, Nov. 20, 1973, as amended at 41 FR 4015, Jan. 28, 1976; 41 FR 10428, Mar. 11, 1976; 44 FR 11754, Mar. 2, 1979; 49 FR 15187, Apr. 18, 1984; 49 FR 23834, June 8, 1984; 50 FR 4133, Jan. 29, 1985; 51 FR 44906, Dec. 15, 1986; 53 FR 12764, Apr. 19, 1988; 55 FR 11013, Mar. 26, 1990; 62 FR 48175, Sept. 15, 1997]

§ 610.13 Purity.

Products shall be free of extraneous material except that which is unavoidable in the manufacturing process described in the approved license. In addition, products shall be tested as provided in paragraphs (a) and (b) of this section.

(a)(1) *Test for residual moisture.* Each lot of dried product shall be tested for residual moisture and shall meet and not exceed established limits as specified by an approved method on file in the product license application. The test for residual moisture may be exempted by the Director, Center for Biologics Evaluation and Research, when deemed not necessary for the continued safety, purity, and potency of the product.

(2) *Records.* Appropriate records for residual moisture under paragraph (a)(1) of this section shall be prepared and maintained as required by the applicable provisions of §§ 211.188 and 211.194 of this chapter.

(b) *Test for pyrogenic substances.* Each lot of final containers of any product intended for use by injection shall be tested for pyrogenic substances by intravenous injection into rabbits as provided in paragraphs (b) (1) and (2) of this section: *Provided,* That notwithstanding any other provision of Subchapter F of this chapter, the test for pyrogenic substances is not required for the following products: Products containing formed blood elements; Cryoprecipitate; Plasma; Source Plasma; Normal Horse Serum; bacterial, viral, and rickettsial vaccines and antigens; toxoids; toxins; allergenic extracts; venoms; diagnostic substances and trivalent organic arsenicals.

(1) *Test dose.* The test dose for each rabbit shall be at least 3 milliliters per kilogram of body weight of the rabbit and also shall be at least equivalent proportionately, on a body weight basis, to the maximum single human dose recommended, but need not exceed 10 milliliters per kilogram of body weight of the rabbit, except that: (i) Regardless of the human dose recommended, the test dose per kilogram of body weight of each rabbit shall be at least 1 milliliter for immune globulins derived from human blood; (ii) for Streptokinase, the test dose shall be at least equivalent proportionately, on a body weight basis, to the maximum single human dose recommended.

(2) *Test procedure, results, and interpretation; standards to be met.* The test for pyrogenic substances shall be performed according to the requirements specified in United States Pharmacopeia XX.

(3) *Retest.* If the lot fails to meet the test requirements prescribed in paragraph (b)(2) of this section, the test may be repeated once using five other rabbits. The temperature rises recorded for all eight rabbits used in testing shall be included in determining whether the requirements are met. The lot meets the requirements for absence of pyrogens if not more than three of the eight rabbits show individual rises in temperature of 0.6 °C or more, and if the sum of the eight individual maximum temperature rises does not exceed 3.7 °C.

(Information collection requirements were approved by the Office of Management and Budget (OMB) and assigned OMB control number 0910–0139)

[38 FR 32056, Nov. 20, 1973, as amended at 40 FR 29710, July 15, 1975; 41 FR 10429, Mar. 11, 1976; 41 FR 41424, Sept. 22, 1976; 44 FR 40289, July 10, 1979; 46 FR 62845, Dec. 29, 1981; 49 FR 15187, Apr. 18, 1984; 50 FR 4134, Jan. 29, 1985; 55 FR 28381, July 11, 1990]

§ 610.14 Identity.

The contents of a final container of each filling of each lot shall be tested for identity after all labeling operations shall have been completed. The identity test shall be specific for each product in a manner that will adequately identify it as the product designated on final container and package labels and circulars, and distinguish it from any other product being processed in the same laboratory. Identity may be established either through the physical or chemical characteristics of the product, inspection by macroscopic or microscopic methods, specific cultural tests, or in vitro or in vivo immunological tests.

§ 610.15 Constituent materials.

(a) *Ingredients, preservatives, diluents, adjuvants.* All ingredients used in a licensed product, and any diluent provided as an aid in the administration of the product, shall meet generally accepted standards of purity and quality. Any preservative used shall be sufficiently nontoxic so that the amount present in the recommended dose of the product will not be toxic to the recipient, and in the combination used it shall not denature the specific substances in the product to result in a decrease below the minimum acceptable potency within the dating period when stored at the recommended temperature. Products in multiple-dose containers shall contain a preservative, except that a preservative need not be added to Yellow Fever Vaccine; Poliovirus Vaccine Live Oral; viral vaccines labeled for use with the jet injector; dried vaccines when the accompanying diluent contains a preservative; or to an Allergenic Product in 50 percent or more volume in volume (v/v) glycerin. An adjuvant shall not be introduced into a product unless there is satisfactory evidence that it does not affect adversely the safety or potency of the product. The amount of aluminum in the recommended individual dose of a biological product shall not exceed:

(1) 0.85 milligrams if determined by assay;

(2) 1.14 milligrams if determined by calculation on the basis of the amount of aluminum compound added; or

(3) 1.25 milligrams determined by assay provided that data demonstrating that the amount of aluminum used is safe and necessary to produce the intended effect are submitted to and approved by the Director, Center for Biologics Evaluation and Research.

(b) *Extraneous protein; cell culture produced vaccines.* Extraneous protein

known to be capable of producing allergenic effects in human subjects shall not be added to a final virus medium of cell culture produced vaccines intended for injection. If serum is used at any stage, its calculated concentration in the final medium shall not exceed 1:1,000,000.

(c) *Antibiotics.* A minimum concentration of antibiotics, other than penicillin, may be added to the production substrate of viral vaccines.

[38 FR 32056, Nov. 20, 1973, as amended at 46 FR 51903, Oct. 23, 1981; 48 FR 13025, Mar. 29, 1983; 48 FR 37023, Aug. 16, 1983; 49 FR 23834, June 8, 1984; 50 FR 4134, Jan. 29, 1985; 51 FR 15607, Apr. 25, 1986; 55 FR 11013, Mar. 26, 1990]

§ 610.16 Total solids in serums.

Except as otherwise provided by regulation, no liquid serum or antitoxin shall contain more than 20 percent total solids.

§ 610.17 Permissible combinations.

Licensed products may not be combined with other licensed products either therapeutic, prophylactic or diagnostic, except as a license is obtained for the combined product. Licensed products may not be combined with nonlicensable therapeutic, prophylactic, or diagnostic substances except as a license is obtained for such combination.

§ 610.18 Cultures.

(a) *Storage and maintenance.* Cultures used in the manufacture of products shall be stored in a secure and orderly manner, at a temperature and by a method that will retain the initial characteristics of the organisms and insure freedom from contamination and deterioration.

(b) *Identity and verification.* Each culture shall be clearly identified as to source strain. A complete identification of the strain shall be made for each new stock culture preparation. Primary and subsequent seed lots shall be identified by lot number and date of preparation. Periodic tests shall be performed as often as necessary to verify the integrity of the strain characteristics and freedom from extraneous organisms. Results of all periodic tests for verification of cultures and determination of freedom from extraneous organisms shall be recorded and retained.

(c) *Cell lines used for manufacturing biological products*—(1) *General requirements.* Cell lines used for manufacturing biological products shall be:

(i) Identified by history;

(ii) Described with respect to cytogenetic characteristics and tumorigenicity;

(iii) Characterized with respect to in vitro growth characteristics and life potential; and

(iv) Tested for the presence of detectable microbial agents.

(2) *Tests.* Tests that are necessary to assure the safety, purity, and potency of a product may be required by the Director, Center for Biologics Evaluation and Research.

(3) *Applicability.* This paragraph applies to diploid and nondiploid cell lines. Primary cell cultures that are not subcultivated and primary cell cultures that are subsequently subcultivated for only a very limited number of population doublings are not subject to the provisions of this paragraph (c).

(d) *Records.* The records appropriate for cultures under this section shall be prepared and maintained as required by the applicable provisions of §§ 211.188 and 211.194 of this chapter.

(Approved by the Office of Management and Budget under control number 0910–0139)

[38 FR 32056, Nov. 20, 1973, as amended at 51 FR 44453, Dec. 10, 1986; 55 FR 11013, Mar. 26, 1990]

§ 610.19 Status of specific products; Group A streptococcus.

The presence of Group A streptococcus organisms and derivatives of Group A streptococcus in Bacterial Vaccines and Bacterial Antigens with ''No U.S. Standard of Potency'' may induce dangerous tissue reactions in humans. Available data demonstrate that they are unsafe as ingredients in products for human use. Group A streptococcus organisms and derivatives of Group A streptococcus are prohibited from Bacterial Vaccines and Bacterial Antigens with ''No U.S. Standard of Potency.'' Any Bacterial Vaccine or Bacterial Antigen with ''No U.S. Standard of Potency'' containing Group A streptococcus organisms or derivatives of Group

A streptococcus in interstate commerce is in violation of section 351 of the Public Health Service Act (42 U.S.C. 262).

[44 FR 1549, Jan. 5, 1979]

Subpart C—Standard Preparations and Limits of Potency

§ 610.20 Standard preparations.

Standard preparations made available by the Center for Biologics Evaluation and Research shall be applied in testing, as follows:

(a) *Potency standards.* Potency standards shall be applied in testing for potency all forms of the following:

ANTIBODIES

Botulism Antitoxin, Type A.
Botulism Antitoxin, Type B.
Botulism Antitoxin, Type E.
Diphtheria Antitoxin.
Histolyticus Antitoxin.
Oedematiens Antitoxin.
Perfringens Antitoxin.
Antipertussis Serum.
Antirabies Serum.
Sordellii Antitoxin.
Staphylococcus Antitoxin.
Tetanus Antitoxin.
Vibrion Septique Antitoxin.

ANTIGENS

Cholera Vaccine, Inaba serotype.
Cholera Vaccine, Ogawa serotype.
Diphtheria Toxin for Schick Test.
Pertussis Vaccine.
Tuberculin, Old.
Tuberculin, Purified Protein Derivative.
Typhoid Vaccine.

BLOOD DERIVATIVE

Thrombin.

(b) *Opacity standard.* The U.S. Opacity Standard shall be applied in estimating the bacterial concentration of all bacterial vaccines. The assigned value of the standard when observed visually is 10 units. The assigned value of the standard when observed with a photometer is (1) 10 units when the wavelength of the filter is 530 millimicrons, (2) 10.6 units when the wavelength of the filter is 650 millimicrons, and (3) 9 units when the wavelength of the filter is 420 millimicrons.

[38 FR 32056, Nov. 20, 1973, as amended at 41 FR 10429, Mar. 11, 1976; 41 FR 18295, May 3, 1976; 49 FR 23834, June 8, 1984; 55 FR 11013, Mar. 26, 1990]

§ 610.21 Limits of potency.

The potency of the following products shall be not less than that set forth below and products dispensed in the dried state shall represent liquid products having the stated limitations.

ANTIBODIES

Diphtheria Antitoxin, 500 units per milliliter.
Tetanus Antitoxin, 400 units per milliliter.
Tetanus Immune Globulin (Human), 50 units of tetanus antitoxin per milliliter.

ANTIGENS

Cholera Vaccine, 8 units each of Inaba and Ogawa serotype antigens per milliliter.
Pertussis Vaccine, 12 units per total human immunizing dose.
Typhoid Vaccine, 8 units per milliliter.

[41 FR 10429, Mar. 11, 1976, as amended at 41 FR 18295, May 3, 1976]

Subpart D—Mycoplasma

§ 610.30 Test for Mycoplasma.

Except as provided otherwise in this subchapter, prior to clarification or filtration in the case of live virus vaccines produced from in vitro living cell cultures, and prior to inactivation in the case of inactivated virus vaccines produced from such living cell cultures, each virus harvest pool and control fluid pool shall be tested for the presence of *Mycoplasma,* as follows:

Samples of the virus for this test shall be stored either (1) between 2 and 8 °C. for no longer than 24 hours, or (2) at −20 °C. or lower if stored for longer than 24 hours. The test shall be performed on samples of the viral harvest pool and on control fluid pool obtained at the time of viral harvest, as follows: No less than 2.0 ml. of each sample shall be inoculated in evenly distributed amounts over the surface of no less than 10 plates of at least two agar media. No less than 1.0 ml. of sample shall be inoculated into each of four tubes containing 10 ml. of a semisolid broth medium. The media shall be such as have been shown to be capable of

detecting known *Mycoplasma* and each test shall include control cultures of at least two known strains of *Mycoplasma,* one of which must be *M. pneumoniae.* One half of the plates and two tubes of broth shall be incubated aerobically at 36 °C. ±1 °C. and the remaining plates and tubes shall be incubated anaerobically at 36 °C. ±1 °C. in an environment of 5–10 percent CO_2 in N_2. Aerobic incubation shall be for a period of no less than 14 days and the broth in the two tubes shall be tested after 3 days and 14 days, at which times 0.5 ml. of broth from each of the two tubes shall be combined and subinoculated on to no less than 4 additional plates and incubated aerobically. Anaerobic incubation shall be for no less than 14 days and the broth in the two tubes shall be tested after 3 days and 14 days, at which times 0.5 ml. of broth from each of the two tubes shall be combined and subinoculated onto no less than four additional plates and incubated anaerobically. All inoculated plates shall be incubated for no less than 14 days, at which time observation for growth of *Mycoplasma* shall be made at a magnification of no less than 300×. If the Dienes Methylene Blue-Azure dye or an equivalent staining procedure is used, no less than a one square cm. plug of the agar shall be excised from the inoculated area and examined for the presence of *Mycoplasma.* The presence of the *Mycoplasma* shall be determined by comparison of the growth obtained from the test samples with that of the control cultures, with respect to typical colonial and microscopic morphology. The virus pool is satisfactory for vaccine manufacture if none of the tests on the samples show evidence of the presence of *Mycoplasma.*

Subpart E—Hepatitis Requirements

§610.40 Test for hepatitis B surface antigen.

(a) *Test sensitivity.* Each donation of blood, plasma, or serum to be used in preparing a biological product shall be tested for the presence of hepatitis B surface antigen by a method of sufficient sensitivity to detect all sera labeled A, (A), B, (B), and C in the Reference Hepatitis B Surface Antigen Panel distributed by the Center for Biologics Evaluation and Research; except that, in emergency situations, a test method of sufficient sensitivity to detect all sera labeled A, (A), and B in the Reference Hepatitis B Surface Antigen Panel may be used and, in dire emergency situations, blood and blood products may be issued without any HB_8 Ag testing, provided that a test otherwise required by this paragraph is performed as soon as possible after issuance of the blood and blood product.

(b) *Procedures.* Only Antibody to Hepatitis B Surface Antigen licensed under this subchapter shall be used in performing the test and the test method(s) used shall be that for which the antibody product is specifically designed to be effective as recommended by the manufacturer in the package insert. The sample of blood, plasma, or serum to be tested shall have been taken from the donor at the time of donation of that unit. The test need not be performed on the day of the withdrawal of the sample. If the radioimmunoassay method is used, it must be performed in one of the following ways:

(1) The complete test is performed at the collection facility.

(2) The test is performed at the collection facility up to the point of counting the radioactivity of the samples, which counting, thereafter, is performed at another facility by personnel from the collection facility or by personnel from the counting facility.

(3) The complete test is performed by the personnel at an establishment licensed to manufacture blood or blood derivatives under section 351(a) of the Public Health Service Act (42 U.S.C. 262(a)), or by a clinical laboratory which meets the standards of the Clinical Laboratories Improvement Act of 1967 (CLIA) (42 U.S.C. 263a), provided the establishment or the clinical laboratory is qualified to perform radioimmunoassay testing for the presence of hepatitis B surface antigen.

(4) Except as provided in this paragraph (b)(4), a collection facility shall not ship any blood product as a biological product or ship such a blood product where it is intended for use in manufacturing a biological product until the test for hepatitis B surface antigen is completed and the written test results are received by the collection facility. Notwithstanding the provisions of §610.1 of this chapter, in the case of an emergency, or as otherwise approved in writing by the Director, Center for Biologics Evaluation and Research, a collection facility may ship a blood product before the test for hepatitis B surface antigen is completed. To

obtain approval for such shipments, the collection facility shall submit a description of the control procedures to be used by both the collection facility and the manufacturing facility to the Director, Center for Biologics Evaluation and Research (HFB–1), Food and Drug Administration, 8800 Rockville Pike, Bethesda, MD 20892. The control procedures to be used by the collection facility and the manufacturing facility shall include, but may not be limited to, a system of communicating the test results to the manufacturing facility, use of specific labeling warnings for the product to ensure that persons handling the shipment know that it may be infectious, procedures for quarantine of the untested or incompletely tested product both at the collection facility and at the manufacturing facility, and a procedure at the manufacturing facility to identify, preclude use of, and dispose of any blood product that is received and later found to be reactive for hepatitis B surface antigen.

(c) *Materials in storage.* All blood, plasma, or serum in storage which has not been tested for the presence of the hepatitis B surface antigen shall be tested as required in paragraphs (a) and (b) of this section before use as a biological product, or before use in the manufacture of a biological product. All blood, plasma, or serum in storage which has been tested for the presence of the hepatitis B surface antigen by a method of second generation sensitivity may be used as a biological product or in manufacture of a biological product, provided it is used on or before March 15, 1976.

(d) *Restrictions on use.* Blood, plasma, or serum that is reactive when tested for hepatitis B surface antigen or that was collected from a donor known to be reactive for hepatitis B surface antigen shall not be used in manufacturing biological products except as provided in paragraphs (d) (1) and (2) of this section.

(1) *Injectable biological products and licensed in vitro diagnostic biological products.* Blood, plasma, or serum that is reactive when tested for hepatitis B surface antigen or that was collected from a donor known to be reactive for hepatitis B surface antigen may be used in manufacturing hepatitis B vaccine and licensed in vitro diagnostic biological products if all of the following conditions are met:

(i) The final product cannot be prepared from blood, plasma, or serum that is nonreactive when tested for hepatitis B surface antigen, due either to the nature or to the scarcity of the final product.

(ii) The label of the source blood, plasma, or serum conspicuously states either that it is reactive when tested for hepatitis B surface antigen and it may transmit viral hepatitis; or that the source blood, plasma, or serum was collected from a donor known to be reactive for hepatitis B surface antigen and it may transmit viral hepatitis, although confirmatory hepatitis testing has not been done.

(iii) The package label of the licensed in vitro diagnostic biological product prepared from such blood, plasma, or serum states conspicuously that either the product was prepared from source material that was reactive when tested for hepatitis B surface antigen and it may transmit viral hepatitis; or that the source material was collected from a donor known to be reactive for hepatitis B surface antigen and it may transmit viral hepatitis, although confirmatory hepatitis testing has not been done.

(iv) The package label of the licensed injectable biological product prepared from such blood, plasma, or serum states that the product has been inactivated.

(v) The Director, Center for Biologics Evaluation and Research (HFB–1), Food and Drug Administration, 8800 Rockville Pike, Bethesda MD 20892, is notified in writing at the time of the shipment, or in the case of repetitive shipments, or April 1 and October 1 of each year, of each shipment of source blood, plasma, or serum for manufacture into hepatitis B vaccine or into a licensed in vitro diagnostic biological product. Such shipments shall not be subject to the requirements of paragraph (b)(3) of this section. Each notification shall identify the kind and amount of source material shipped, the name and address of the consignee, the date of shipment, and the manner in which the source material is labeled.

(2) *Unlicensed in vitro diagnostic biological products.* Blood, plasma, or serum that is reactive when tested for hepatitis B surface antigen or that was collected from a donor known to be reactive for hepatitis B surface antigen may be used in manufacturing unlicensed in vitro diagnostic biological products including clinical chemistry control reagents if all of the following conditions are met:

(i) The final product cannot be prepared from blood, plasma, or serum that is nonreactive when tested for hepatitis B surface antigen, due either to the nature or to the scarcity of the final product.

(ii) The label of the source blood, plasma, or serum states conspicuously that either it is reactive when tested for hepatitis B surface antigen and it may transmit viral hepatitis; or that the source blood, plasma, or serum was collected from a donor known to be reactive for hepatitis B surface antigen and it may transmit viral hepatitis, although confirmatory hepatitis testing has not been done.

(iii) The manufacturer of the source blood, plasma, or serum obtains written assurance from the manufacturer(s) of the final unlicensed product that package labels of all unlicensed products will conspicuously state, as required by §809.10(a)(4) of this chapter, that the product was prepared from blood, plasma, or serum that was reactive when tested for hepatitis B surface antigen and it may transmit viral hepatitis; or that the source material was collected from a donor known to be reactive for hepatitis B surface antigen and it may transmit viral hepatitis, although confirmatory hepatitis testing has not been done.

(iv) At the time of shipment, the Director, Center for Biologics Evaluation and Research (HFB–1), Food and Drug Administration, 8800 Rockville Pike, Bethesda, MD 20892, is notified in writing of each shipment of source blood, plasma, or serum signifying the kind and the amount of source material shipped, the name and address of the consignee, the date of shipment, and the manner in which such source material was labeled. Such shipments shall not be subject to the requirements of paragraph (b)(3) of this section.

(e) *Manufacturing responsibility.* When the radioimmunoassay method for hepatitis B surface antigen testing is performed by personnel other than those of the facility collecting the blood, plasma, or serum, as provided in paragraph (b) of this section, it shall not be considered as divided manufacturing as described in §610.63, provided the following conditions are met:

(1) The collecting facility has obtained a written agreement that the testing laboratory will permit authorized representatives of the Food and Drug Administration to inspect its testing procedures and facilities during reasonable business hours.

(2) The testing laboratory will participate in any proficiency testing programs undertaken by the Center for Biologics Evaluation and Research, Food and Drug Administration.

(f) The information collection requirements in paragraph (d) of this section were approved by the Office of Management and Budget and assigned OMB control number 0910–0136.

(Information collection requirements contained in paragraph (b)(4) were approved by the Office of Management and Budget under control number 0910–0168)

[40 FR 29710, July 15, 1975, as amended at 48 FR 23181, May 24, 1983; 49 FR 23834, June 8, 1984; 49 FR 26718, June 29, 1984; 51 FR 15607, Apr. 25, 1986; 55 FR 11013 and 11014, Mar. 26, 1990]

§610.41 History of hepatitis B surface antigen.

A person known to have previously tested positive for hepatitis B surface antigen, testing positive, or both, may not serve as a donor of human blood, plasma, or serum, except that under §640.120 of this chapter, such a donor may serve as a source of hepatitis B surface antigen for the manufacture of hepatitis B vaccine or the preparation of a diagnostic product for laboratory tests, or a person known to have previously tested positive for hepatitis B surface antigen may serve as a source of antibody to hepatitis B surface antigen for the preparation of a biological product or a diagnostic product for laboratory tests.

[48 FR 23182, May 24, 1983, as amended at 57 FR 10814, Mar. 31, 1992]

§ 610.45 Human Immunodeficiency Virus (HIV) requirements.

(a) *Testing requirements.* (1) Each donation of human blood or blood components intended for use in preparing a product shall be tested for antibody to HIV by a test approved for such use by FDA, except as otherwise approved in writing by FDA. When the test for antibody to HIV is required, blood and blood products may be issued before the results of the test for antibody to HIV are available only in dire emergency situations or as otherwise approved in writing by FDA and, provided the test required by this paragraph is performed as soon as possible after issuance of the blood or blood product.

(2) Tests approved by FDA for the screening of blood and blood components for evidence of HIV may only be used in place of a test for antibody to HIV to satisfy the requirements of this section and related sections if so specified by FDA.

(b) *Testing responsibility.* The test for antibody to HIV shall be performed by the collection facility, by personnel of an establishment licensed to manufacture blood or blood derivatives under section 351(a) of the Public Health Service Act (42 U.S.C. 262(a)), or by a clinical laboratory which meets the standards of the Clinical Laboratory Improvement Act of 1967 (CLIA) (42 U.S.C. 263a), provided the establishment or clinical laboratory is qualified to perform the test.

(c) *Restrictions on use.* (1) Blood, plasma, or other blood components that are repeatably reactive to a test for antibody to HIV or that were collected from a donor whose blood is known to be repeatably reactive to a test for antibody to HIV, shall not be shipped or used to prepare any product, including products not subject to licensure; except that such blood and blood components shall be shipped or used only for purposes and under conditions specifically approved in writing by FDA.

(2) The restrictions on use contained in this paragraph shall not apply in the following cases:

(i) Blood and blood components testing repeatably reactive or from a donor whose blood is known to be repeatably reactive that are shown to be negative for evidence of HIV infection by a method or process approved for such use by FDA;

(ii) The distribution of blood, plasma, or serum samples, except when intended for use in the manufacture of a product;

(iii) The in-house use of blood and blood components for research purposes; or

(iv) The distribution of blood and blood components for research purposes, if not distributed by sale, barter, or exchange.

(d) For a donor whose test results for antibody to HIV are repeatedly reactive or otherwise determined to be unsuitable when tested in accordance with paragraph (a) of this section, the blood establishment shall comply, as applicable, with §§ 610.46 and 610.47.

[53 FR 116, Jan. 5, 1988, as amended at 61 FR 47423, Sept. 9, 1996]

§ 610.46 "Lookback" requirements.

(a) *Quarantine and notification.* (1) All blood and plasma establishments are required to take appropriate action when a donor of Whole Blood, blood components, Source Plasma and Source Leukocytes tests repeatedly reactive for antibody to human immunodeficiency virus (HIV), or otherwise is determined to be unsuitable when tested in accordance with § 610.45. For Whole Blood, blood components, Source Plasma and Source Leukocytes collected from that donor within the 5 years prior to the repeatedly reactive test, if intended for transfusion, or collected within the 6 months prior to the repeatedly reactive test, if intended for further manufacture into injectable products, except those products exempt from quarantine in accordance with § 610.46(c), the blood establishment shall promptly, within 72 hours:

(i) Quarantine all such Whole Blood, blood components, Source Plasma and Source Leukocytes from previous collections held at that establishment; and

(ii) Notify consignees of the repeatedly reactive HIV screening test results so that all Whole Blood, blood components, Source Plasma and Source Leukocytes from previous collections they hold are quarantined.

(2) Consignees notified in accordance with paragraph (a)(1)(ii) of this section

shall quarantine Whole Blood, blood components, Source Plasma and Source Leukocytes held at that establishment except as provided in paragraph (c) of this section.

(b) *Further testing and notification of consignees of results.* Blood establishments that have collected Whole Blood, blood components, Source Plasma or Source Leukocytes from a donor as described in paragraph (a) of this section shall perform a licensed, more specific test for HIV on the donor's blood, and in the case of distributed products, further shall notify the consignee(s) of the results of this test, within 30 calendar days after the donor's repeatedly reactive test. Pending the availability of a licensed, more specific test for HIV–2, a second, different screening test for antibody to HIV–2 shall be used along with a licensed, more specific test for HIV–1.

(c) *Exemption from quarantine.* Products intended for transfusion need not be held in quarantine if a determination has been made that the Whole Blood, blood components, Source Plasma or Source Leukocytes was collected more than 12 months prior to the donor's most recent negative antibody screening test when tested in accordance with §610.45. Pooled Source Plasma and Source Leukocytes are exempt from quarantine.

(d) *Release from quarantine.* Whole Blood, blood components, Source Plasma and Source Leukocytes intended for transfusion or further manufacture which have been quarantined under paragraph (a) of this section may be released if the donor is subsequently tested for antibody to HIV as provided in paragraph (b) of this section and the test result is negative, absent other informative test results.

(e) Actions under this section do not constitute a product recall as defined in §7.3(g) of this chapter.

[61 FR 47423, Sept. 9, 1996]

§610.47 "Lookback" notification requirements for transfusion services.

(a) Transfusion services that are not subject to the Health Care Financing Administration's regulations on conditions of Medicare participation for hospitals (42 CFR part 482) are required to take appropriate action in accordance with paragraphs (b) and (c) of this section when a recipient has received Whole Blood or blood components from a donor determined to be unsuitable when tested for human immunodeficiency virus (HIV) infection in accordance with §610.45 and the results of the additional tests as provided for in §610.46(b) are positive.

(b) *Notification of recipients of prior transfusion.* If the transfusion service has administered Whole Blood or blood components as described in paragraph (a) of this section, the transfusion service shall notify the recipient's attending physician (physician of record) and ask him or her to inform the recipient of the need for HIV testing and counseling. If the physician is unavailable or declines to notify the recipient, the transfusion service shall notify the recipient and inform the recipient of the need for HIV testing and counseling. The notification process shall include a minimum of three attempts to notify the recipient and be completed within a maximum 8 weeks of receipt of the result of the licensed, more specific test for HIV. The transfusion service is responsible for notification, including basic explanations to the recipient and referral for counseling, and shall document the notification or attempts to notify the attending physician or the recipient, pursuant to §606.160 of this chapter.

(c) *Notification to legal representative or relative.* If the transfusion recipient has been adjudged incompetent by a State court, the transfusion service or physician must notify a legal representative designated in accordance with State law. If the transfusion recipient is competent, but State law permits a legal representative or relative to receive the information on the recipient's behalf, the transfusion service or physician must notify the recipient or his or her legal representative or relative. If the transfusion recipient is deceased, the transfusion service or physician must continue the notification process and inform the deceased recipient's legal representative or relative. Reasons for notifying the recipient's relative or legal representative on his or her behalf shall be documented pursuant to §606.160 of this chapter.

[61 FR 47423, Sept. 9, 1996]

Subpart F—Dating Period Limitations

§ 610.50 Date of manufacture.

The date of manufacture shall be determined as follows:

(a) For products for which an official standard of potency is prescribed in either § 610.20 or § 610.21, or which are subject to official potency tests, the date of initiation by the manufacturer of the last valid potency test.

(b) For products that are not subject to official potency tests, (1) the date of removal from animals, (2) the date of extraction, (3) the date of solution, (4) the date of cessation of growth, or (5) the date of final sterile filtration of a bulk solution, whichever is applicable.

[38 FR 32056, Nov. 20, 1973, as amended at 42 FR 27582, May 31, 1977]

§ 610.53 Dating periods for licensed biological products.

(a) *General.* The minimum dating periods in paragraph (c) of this section are based on data relating to usage, clinical experience, or laboratory tests that establish the reasonable period beyond which the product cannot be expected to yield its specific results and retain its safety, purity, and potency, provided the product is maintained at the recommended temperatures. The standards prescribed by the regulations in this subchapter are designed to ensure the continued safety, purity, and potency of the products and are based on the dating periods set forth in paragraph (c) of this section. Package labels for each product shall recommend storage at the stated temperatures.

(b) *When the dating period begins.* The dating period for a product shall begin on the date of manufacture, as prescribed in § 610.50. The dating period for a combination of two or more products shall be no longer than the dating period of the component with the shortest dating period.

(c) *Table of dating periods.* In using the table in this paragraph, a product in column A may be stored by the manufacturer at the prescribed temperature and length of time in either column B or C, plus the length of time in column D. The dating period in column D shall be applied from the day the product leaves the manufacturer's storage, provided the product has not exceeded its maximum storage period, as prescribed in column B or C. If a product is held in the manufacturer's storage beyond the period prescribed, the dating period for the product being distributed shall be reduced by a corresponding period.

A	B	C	D
Product	Manufacturer's storage period 1 to 5 °C (unless otherwise stated)	Manufacturer's storage period 0 °C or colder (unless otherwise stated)	Dating period after leaving manufacturer's storage when stored at 2 to 8 °C (unless otherwise stated)
Adenovirus Vaccine Live Oral	6 months	Not applicable	6 months.
Albumin (Human)	3 years	.....do	(a) 5 years.
	.....do	.....do	(b) 3 years, provided labeling recommends storage at room temperature, no warmer than 37 °C.
	Not applicable	.....do	(c) 10 years, if in a hermetically sealed metal container and provided labeling recommends storage between 2 and 8 °C.
Allergenic Extracts labeled "No U.S. Standard of Potency":			
1. With 50 percent or more glycerin	3 years	.....do	3 years.
2. With less than 50 percent glycerin	18 months	.....do	18 months.
3. Products for which cold storage conditions are inappropriate.	Not applicable	.....do	18 months (from date of manufacture), provided labeling recommends storage at 30 °C or colder.
4. Powders and tablets	.....do	.....do	5 years (from date of manufacture), provided labeling recommends storage at 30 °C or colder.
5. Freeze-dried products:			
a. Unreconstituted	.....do	.....do	4 years (from date of manufacture).
b. Reconstituted	.....do	.....do	18 months (cannot exceed 4-year unreconstituted dating period plus an additional 12 months).

A	B	C	D
Product	Manufacturer's storage period 1 to 5 °C (unless otherwise stated)	Manufacturer's storage period 0 °C or colder (unless otherwise stated)	Dating period after leaving manufacturer's storage when stored at 2 to 8 °C (unless otherwise stated)
Allergenic Extracts, Alum Precipitated labeled ''No U.S. Standard of Potency''.	18 months	do	18 months.
Anthrax Vaccine Adsorbed	2 years	do	1 year.
Antibody to Hepatitis B Surface Antigen:			
1. Antibody to Hepatitis B Surface Antigen.	6 months	do	6 months.
2. Lyophilized coated red blood cells	do	do	Do.
3. Enzyme conjugated products	do	do	Do.
Iodinated (^{125}I) products	Not applicable	do	45 days (from date of manufacture).
Antihemophilic Factor (Human)	do	do	1 year (from date of manufacture).
Anti-Human Globulin Liquid	do	do	2 years.
Anti-Inhibitor Coagulant Complex	do	do	Do.
Antirabies Serum	1 year	do	Do.
Antivenin (*Crotalidae*) Polyvalent	do	do	5 years with an initial 10 percent excess of potency, provided labeling recommends storage at 37 ° C or colder.
Antivenin (*Latrodectus Mactans*)	do	do	5 years with an initial 10 percent excess of potency.
Antivenin (*Micurus fulvius*)	do	do	Do.
Asparaginase	Not applicable	do	18 months from the date of the last valid potency test.
BCG Vaccine	1 year	Not applicable	6 months.
Blood Grouping Reagents			
1. Liquid	Not applicable	Not applicable	2 years.
2. Dried	1 year	2 years	5 years.
Blood Group Substance AB	do	do	2 years.
Blood Group Substance A	do	do	Do.
Blood Group Substance B	do	do	Do.
Botulism Antitoxin	do	Not applicable	5 years with an initial 20 percent excess of potency.
Cholera Vaccine	do	do	18 months.
Coccidioidin	do	do	3 years.
Collagenase	Not applicable	do	4 years (from date of manufacture), provided labeling recommends storage at 37 °C or colder.
Cryoprecipitated AFH	do	do	12 months from the date of collection of source blood, provided labeling recommends storage at −18 °C or colder.
Diphtheria Antitoxin:			
1. Liquid	1 year	do	5 years with an initial 20 percent excess of potency.
2. Dried	do	2 years	5 years with an initial 10 percent excess of potency.
Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed.	do	Not applicable	18 months.
Diphtheria and Tetanus Toxoids, Adsorbed.	do	do	2 years.
Diphtheria Toxin for Schick Test	do	do	1 year.
Diphtheria Toxoid	do	do	2 years.
Diphtheria Toxoid Adsorbed	do	2 years	Do.
Diphtheria Toxoid-Schick Test Control	Not applicable	Not applicable	1 year.
Factor IX Complex	do	do	1 year (from date of manufacture).
Fibrinolysin (Human)	1 year	2 years	2 years.
Fibrinolysin and Desoxyribonuclease Combined (Bovine).	do	do	3 years, provided labeling recommends storage at 30 °C or colder.
Fibrinolysin and Desoxyribonuclease Combined (Bovine) with Chloramphenicol.	do	do	Do.
Hepatitis B Surface Antigen:			
1. Unlyophilized coated red blood cells.	Not applicable	do	14 days (from date of manufacture).
2. Iodinated (^{125}I) product	do	do	45 days (from date of manufacture).
3. Enzyme conjugated product	6 months	do	6 months.
Histoplasmin	1 year	Not applicable	2 years.
Immunoglobulins:			
1. Hepatitis B Immune Globulin (Human).	Not applicable	do	1 year.
2. Immune Globulin (Human)	3 years	do	3 years.

A	B	C	D
Product	Manufacturer's storage period 1 to 5 °C (unless otherwise stated)	Manufacturer's storage period 0 °C or colder (unless otherwise stated)	Dating period after leaving manufacturer's storage when stored at 2 to 8 °C (unless otherwise stated)
3. Immune Globulin Intravenous (Human).	Not applicable	do	1 year.
4. Lymphocyte Immune Globulin, Anti-Thymocyte Globulin (Equine).	do	Not applicable	2 years.
5. Pertussis Immune Globulin (Human).	3 years	do	3 years from date the dried or frozen bulk product is placed in final solution.
6. Rabies Immune Globulin (Human)	1 year	do	1 year.
7. Rh_o(D) Immune Globulin (Human)	6 months	do	6 months.
8. Tetanus Immune Globulin (Human)	1 year	do	3 years with an initial 10 percent excess of potency.
9. Vaccinia Immune Globulin (Human).	3 years	do	3 years.
10. Varicella-Zoster Immune Globulin (Human).	Not applicable	do	1 year.
Hepatitis B Vaccine	2 years at 2 to 8 °C.	Not applicable	3 years.
Influenza Virus Vaccine	1 year	do	18 months.
Limulus Amebocyte Lysate	Not applicable	Not applicable	18 months (from date of manufacture).
Measles, Mumps, and Rubella Virus Vaccine Live.	do	1 year (−20 °C or colder).	1 year.
Measles and Mumps Virus Vaccine Live	do	do	1 year.
Measles and Rubella Virus Vaccine Live	do	do	Do.
Measles Live and Smallpox Vaccine	Not applicable	do	1 year (from date of manufacture).
Measles Virus Vaccine Live	do	do	1 year.
Meningococcal Polysaccharide Vaccine Group A:			
1. Final bulk powder	do	2 years (−20 °C or colder).	Not applicable.
2. Final container	Not applicable	3 years (−20 °C or colder).	2 years.
Meningococcal Polysaccharide Vaccine Group C:			
1. Final bulk powder	do	2 years (−20 °C or colder).	Not applicable.
2. Final container	do	3 years (−20 °C or colder).	2 years.
Meningococcal Polysaccharide Vaccine Groups A and C combined:			
1. Final bulk powder	do	2 years (−20 °C or colder).	Not applicable.
2. Final container	do	3 years (−20 °C or colder).	2 years.
Meningococcal Polysaccharide Vaccine Groups A, C, Y, and W135 combined:			
1. Final bulk power	do	2 years (−20 °C or colder).	Not applicable.
2. Final container	do	3 years (−20 °C or colder).	2 years.
Mumps Skin Test Antigen	6 months	Not applicable	18 months.
Mumps Virus Vaccine Live	Not applicable	1 year (−20 °C or colder).	1 year.
Normal Horse Serum	1 year	2 years	5 years.
Pertussis Vaccine	do	Not applicable	18 months.
Pertussis Vaccine Adsorbed	do	do	Do.
Plague Vaccine	do	do	Do.
Plasma products:			
1. Fresh Frozen Plasma	Not applicable	do	1 year from date of collection of source blood (−18 °C or colder).
2. Liquid Plasma	do	do	(a) 26 days from date of collection of source blood (between 1 and 6 °C). (b) 40 days from date of collection of source blood only when CPDA–1 solution is used as the anticoagulant (between 1 and 6 °C).
3. Plasma	do	do	5 years from date of collection of source blood (−18 °C or colder).

A	B	C	D
Product	Manufacturer's storage period 1 to 5 °C (unless otherwise stated)	Manufacturer's storage period 0 °C or colder (unless otherwise stated)	Dating period after leaving manufacturer's storage when stored at 2 to 8 °C (unless otherwise stated)
4. Platelet Rich Plasma	.....do	.....do	72 hours from time of collection of source blood, provided labeling recommends storage (20 to 24 °C or between 1 and 6 °C). 5 days if certain approved containers are used (20 to 24 °C).
5. Source Leukocytes	.....do	.....do	In lieu of expiration date, the collection date shall appear on the label.
6. Source Plasma	.....do	.....do	10 years (at the recommended storage temperature stated on the label).
7. Therapeutic Exchange Plasma	.....do	.....do	10 years.
Plasma Protein Fraction (Human)	1 year	.....do	(a) 5 years. (b) 3 years provided labeling recommends storage at room temperature, no warmer than 30 °C).
Platelets	Not applicable	.....do	72 hours from time of collection of source blood, provided labeling recommends storage at 20 to 24 °C or between 1 and 6 °C. 5 days if certain approved containers are used (20 to 24 °C).
Pneumococcal Vaccine Polyvalent:			
1. Final bulk powder	.....do	24 months after potency assay (−20 °C or colder).	Not applicable.
2. Final container	.....do	Not applicable	2 years (from date of manufacture).
Poliovirus Vaccine Inactivated	1 year	.....do	1 year.
Poliovirus Vaccine Live Oral Trivalent:			
1. Frozen	Not applicable	1 year (−10 °C or colder).	1 year, provided labeling recommends storage at a temperature which will maintain ice continuously in a solid state.
2. Liquid	.....do	Not applicable	30 days, provided labeling recommends storage between 2 and 8 °C and container has been unopened.
Poliovirus Vaccine Live Oral Type I:			
1. Frozen	.....do	1 year (−10 °C or colder).	1 year, provided labeling recommends storage at a temperature which will maintain ice continuously in a solid state.
2. Liquid	.....do	Not applicable	30 days, provided labeling recommends storage between 2 and 8 °C and container has been unopened.
Poliovirus Vaccine Live Oral Type II:			
1. Frozen	.....do	1 year (−10 °C or colder).	1 year, provided labeling recommends storage at a temperature which will maintain ice continuously in a solid state.
2. Liquid	.....do	Not applicable	30 days, provided labeling recommends storage between 2 and 8 °C and container has been unopened.
Poliovirus Vaccine Live Oral Type III:			
1. Frozen	.....do	1 year (−10 °C or colder).	1 year, provided labeling recommends storage at a temperature which will maintain ice continuously in a solid state.
2. Liquid	.....do	Not applicable	30 days, provided labeling recommends storage between 2 and 8 °C and container has been unopened.
Polyvalent bacterial antigens with "No U.S. Standard of Potency" liquid.	1 year	.....do	18 months.
Polyvalent bacterial vaccines with "No U.S. Standard of Potency" liquid.	.....do	.....do	Do.
Rabies Vaccine:			
1. Dried	.....do	2 years	Do.
2. Liquid	3 months	Not applicable	6 months.
Reagent red blood cells	Not applicable	Not applicable	Thirty-five days from earliest date of collection if kept in liquid form (indefinite storage of reagent red blood cell source material at −65 °C or colder).

A	B	C	D
Product	Manufacturer's storage period 1 to 5 °C (unless otherwise stated)	Manufacturer's storage period 0 °C or colder (unless otherwise stated)	Dating period after leaving manufacturer's storage when stored at 2 to 8 °C (unless otherwise stated)
ACD Red Blood Cells	.....do	.....do	(a) 21 days from date of collection of source blood, provided labeling recommends storage between 1 and 6 °C and the hermetic seal is not broken during processing. (b) 24 hours after plasma removal, provided labeling recommends storage between 1 and 6 °C and the hermetic seal is broken during processing.
CPD Red Blood Cells	.....do	.....do	(a) 21 days from date of collection of source blood, provided labeling recommends storage between 1 and 6 °C and the hermetic seal is not broken during processing. (b) 24 hours after plasma removal, provided labeling recommends storage between 1 and 6 °C and the hermetic seal is broken during processing.
CPDA–1 Red Blood Cells	.....do	.....do	(a) 35 days from date of collection of source blood, provided labeling recommends storage between 1 and 6 °C and the hermetic seal is not broken during processing. (b) 24 hours after plasma removal, provided labeling recommends storage between 1 and 6 °C and the hermetic seal is broken during processing.
Red Blood Cells Deglycerolized	.....do	.....do	24 hours after removal from storage at −65 °C or colder, provided labeling recommends storage between 1 and 6 °C.
Red Blood Cells Frozen	.....do	.....do	3 years from date of collection of source blood, provided labeling recommends storage at −65 °C or colder.
Rubella and Mumps Virus Vaccine Live	.....do	1 year (−20 °C or colder).	1 year.
Rubella Virus Vaccine Live	.....do	.....do	Do.
Skin Test Antigens for Cellular Hypersensitivity.	6 months	Not applicable	Do.
Smallpox Vaccine:			
1. Liquid	Not applicable	9 months (−10 °C or colder, if product is maintained as glycerinated or equivalent vaccine in bulk or final containers).	3 months, provided labeling recommends storage at 0 °C or colder.
2. Dried	6 months	Not applicable	18 months.
Streptokinase	Not applicable	.....do	Do.
Tetanus and Diphtheria Toxoids Adsorbed for Adult Use.	1 year	.....do	2 years.
Tetanus Antitoxin:			
1. Liquid	.....do	.....do	5 years with an initial 20 percent excess or potency.
2. Dried	.....do	2 years	5 years with an initial 10 percent excess or potency.
Tetanus Toxoid	.....do	Not applicable	2 years.
Tetanus Toxoid Adsorbed	.....do	.....do	Do.
Thrombin	.....do	2 year	3 years.
Thrombin Impregnated Pad	Not applicable	Not applicable	1 year, or 6 months at 20 to 24 °C.
Tuberculin:			
1. Purified Protein Derivative, diluted	6 months	.....do	1 year.
2. Old or Purified Protein Derivative dried on multiple puncture device.	1 year (not to exceed 30 °C; do not refrigerate).	.....do	2 years, provided labeling recommends storage at a temperature not to exceed 30 °C. Do not refrigerate.
3. Old on multiple puncture device	.....do	.....do	Do.
Typhoid Vaccine	1 year	.....do	18 months.

A	B	C	D
Product	Manufacturer's storage period 1 to 5 °C (unless otherwise stated)	Manufacturer's storage period 0 °C or colder (unless otherwise stated)	Dating period after leaving manufacturer's storage when stored at 2 to 8 °C (unless otherwise stated)
ACD Whole Blood	Not applicable	do	21 days from date of collection, provided labeling recommends storage between 1 and 6 °C.
CPD Whole Blood	do	do	Do.
CPDA–1 Whole Blood	do	do	35 days from date of collection, provided labeling recommends storage between 1 and 6 °C.
Heparin Whole Blood	do	do	48 hours from date of collection, provided labeling recommends storage between 1 and 6 °C.
Yellow Fever Vaccine	do	1 year (−20 °C or colder).	1 year, provided labeling recommends storage at 5 °C or colder.

(d) *Exemptions.* Exemptions or modifications shall be made only upon written approval, in the form of a supplement of the product license, issued by the Director, Center for Biologics Evaluation and Research (HFB–1).

[50 FR 4134, Jan. 29, 1985, as amended at 51 FR 15607, Apr. 25, 1986; 51 FR 19750, June 2, 1986; 52 FR 37450, Oct. 7, 1987; 53 FR 12764, Apr. 19, 1988; 55 FR 11014, Mar. 26, 1990; 59 FR 49351, Sept. 28, 1994; 62 FR 15110, Mar. 31, 1997]

Subpart G—Labeling Standards

§ 610.60 Container label.

(a) *Full label.* The following items shall appear on the label affixed to each container of a product capable of bearing a full label:

(1) The proper name of the product;

(2) The name, address, and license number of manufacturer;

(3) The lot number or other lot identification;

(4) The expiration date;

(5) The recommended individual dose, for multiple dose containers.

(6) The statement: ''Caution: Federal law prohibits dispensing without prescription,'' for prescription biologicals.

(b) *Package label information.* If the container is not enclosed in a package, all the items required for a package label shall appear on the container label.

(c) *Partial label.* If the container is capable of bearing only a partial label, the container shall show as a minimum the name (expressed either as the proper or common name), the lot number or other lot identification and the name of the manufacturer; in addition, for multiple dose containers, the recommended individual dose. Containers bearing partial labels shall be placed in a package which bears all the items required for a package label.

(d) *No container label.* If the container is incapable of bearing any label, the items required for a container label may be omitted, provided the container is placed in a package which bears all the items required for a package label.

(e) *Visual inspection.* When the label has been affixed to the container a sufficient area of the container shall remain uncovered for its full length or circumference to permit inspection of the contents.

[38 FR 32056, Nov. 20, 1973, as amended at 47 FR 22518, May 25, 1982]

§ 610.61 Package label.

The following items shall appear on the label affixed to each package containing a product:

(a) The proper name of the product;

(b) The name, address, and license number of manufacturer;

(c) The lot number or other lot identification;

(d) The expiration date;

(e) The preservative used and its concentration, or if no preservative is used and the absence of a preservative is a safety factor, the words ''no preservative'';

(f) The number of containers, if more than one;

(g) The amount of product in the container expressed as (1) the number of doses, (2) volume, (3) units of potency,

(4) weight, (5) equivalent volume (for dried product to be reconstituted), or (6) such combination of the foregoing as needed for an accurate description of the contents, whichever is applicable;

(h) The recommended storage temperature;

(i) The words ''Shake Well'', ''Do not Freeze'' or the equivalent, as well as other instructions, when indicated by the character of the product;

(j) The recommended individual dose if the enclosed container(s) is a multiple-dose container;

(k) The route of administration recommended, or reference to such directions in an enclosed circular;

(l) Known sensitizing substances, or reference to an enclosed circular containing appropriate information;

(m) The type and calculated amount of antibiotics added during manufacture;

(n) The inactive ingredients when a safety factor, or reference to an enclosed circular containing appropriate information;

(o) The adjuvant, if present;

(p) The source of the product when a factor in safe administration;

(q) The identity of each microorganism used in manufacture, and, where applicable, the production medium and the method of inactivation, or reference to an enclosed circular containing appropriate information;

(r) Minimum potency of product expressed in terms of official standard of potency or, if potency is a factor and no U.S. standard of potency has been prescribed, the words ''No U.S. standard of potency.''

(s) The statement: ''Caution: Federal law prohibits dispensing without prescription,'' for prescription biologicals.

[38 FR 32056, Nov. 20, 1973, as amended at 47 FR 22518, May 25, 1982; 55 FR 10423, Mar. 21, 1990]

§ 610.62 Proper name; package label; legible type.

(a) *Position.* The proper name of the product on the package label shall be placed above any trademark or trade name identifying the product and symmetrically arranged with respect to other printing on the label.

(b) *Prominence.* The point size and typeface of the proper name shall be at least as prominent as the point size and typeface used in designating the trademark and trade name. The contrast in color value between the proper name and the background shall be at least as great as the color value between the trademark and trade name and the background. Typography, layout, contrast, and other printing features shall not be used in a manner that will affect adversely the prominence of the proper name.

(c) *Legible type.* All items required to be on the container label and package label shall be in legible type. ''Legible type'' is type of a size and character which can be read with ease when held in a good light and with normal vision.

§ 610.63 Divided manufacturing responsibility to be shown.

If two or more establishments participate in the manufacture of a product, the name, address, and license number of each must appear on the package label, and on the label of the container if capable of bearing a full label.

§ 610.64 Name and address of distributor.

The name and address of the distributor of a product may appear on the label provided that the name, address, and license number of the manufacturer also appears on the label and the name of the distributor is qualified by one of the following phrases: ''Manufactured for_____'', ''Distributed by _____'', ''Manufactured by _____ for _____'', ''Manufactured for _____ by _____'', ''Distributor: _____'', or ''Marketed by _____''. The qualifying phrases may be abbreviated.

[61 FR 57330, Nov. 6, 1996]

§ 610.65 Products for export.

Labels on packages or containers of products for export may be adapted to meet specific requirements of the regulations of the country to which the product is to be exported provided that in all such cases the minimum label requirements prescribed in § 610.60 are observed.

PART 640—ADDITIONAL STANDARDS FOR HUMAN BLOOD AND BLOOD PRODUCTS

AUTHORITY: 21 U.S.C. 321, 351, 352, 353, 355, 360, 371; 42 U.S.C. 216, 262, 263, 263a, 264.

SOURCE: 38 FR 32089, Nov. 20, 1973, unless otherwise noted.

CROSS REFERENCES: For U.S. Customs Service regulations relating to viruses, serums, and toxins, see 19 CFR 12.21–12.23. For U.S. Postal Service regulations relating to the admissibility to the United States mails see parts 124 and 125 of the Domestic Mail Manual, that is incorporated by reference in 39 CFR part 111.

Subpart A—Whole Blood

§ 640.1 Whole Blood.

The proper name of this product shall be Whole Blood. Whole Blood is defined as blood collected from human donors for transfusion to human recipients.

[38 FR 32089, Nov. 20, 1973, as amended at 50 FR 4138, Jan. 29, 1985]

§ 640.2 General requirements.

(a) *Manufacturing responsibility.* All manufacturing of Whole Blood, including donor examination, blood collection, laboratory tests, labeling, storage and issue, shall be done under the supervision and control of the same licensed establishment except that the Director, Center for Biologics Evaluation and Research, may approve arrangements, upon joint request of two or more licensed establishments, which he finds are of such a nature as to assure compliance otherwise with the provisions of this subchapter.

(b) *Periodic check on sterile technique.* Where blood is collected in an open system, that is, where the blood container is entered, at least one container of such blood that upon visual examination appears normal shall be tested each month between the 18th and 24th day after collection (between the 32d and 38th day after collection when CPDA–1 solution is used as the anticoagulant), as a continuing check on technique of blood collection, as follows: The test shall be performed with a total sample of no less than 10 milliliters of blood and a total volume of fluid thioglycollate medium 10 times the volume of the sample of blood. The test sample shall be inoculated into one or more test vessels in a ratio of blood to medium of 1 to 10 for each vessel, mixed thoroughly, incubated for 7 to 9 days at a temperature of 30 to 32 °C, and examined for evidence of growth of microorganisms every workday throughout the test period. On the third, fourth, or fifth day, at least 1 milliliter of material from each test vessel shall be subcultured in additional test vessels containing the same culture medium and in such proportion as will permit significant visual inspection, mixed thoroughly, incubated for 7 to 9 days at a temperature of 30 to 32 °C, and examined for evidence of growth of microorganisms every workday throughout the test period. If growth is observed in any test vessel, the test shall be repeated to rule out faulty test procedure, using another sample of blood from either, (1) the container from which the initial test sample was taken; (2) the residual cells or plasma from that blood; or (3) two different containers of blood, each 18 to 24 days old (32 to 38 days old when CPDA–1 solution is used as the anticoagulant) and each tested separately. The formula for Fluid Thioglycollate Medium shall be as prescribed in §610.12(e)(1) of this chapter. Media and design of container shall meet the requirements prescribed in §610.12(e)(2)(i) and (ii) of this chapter. In lieu of performing one test using an incubation temperature of 30 to 32 °C, two tests may be performed: Each in all respects as prescribed in this paragraph, one at an incubation temperature of 18 to 22 °C and one at an incubation temperature of 35 to 37 °C.

(c) *Final container.* The original blood container shall be the final container and shall not be entered prior to issue for any purpose except for blood collection. Such container shall be uncolored and transparent to permit visual inspection of the contents and any closure shall be such as will maintain an hermetic seal and prevent contamination of the contents. The container material shall not interact with the contents under the customary conditions of storage and use, in such a manner as to have an adverse effect upon the safety, purity, or potency of the blood.

(d) [Reserved]

(e) *Reissue of blood.* Blood that has been removed from storage controlled by a licensed establishment shall not be reissued by a licensed establishment unless the following conditions are observed:

(1) The container has a tamper-proof seal when originally issued and this seal remains unbroken;

(2) An original pilot sample is properly attached and has not been removed, except that blood lacking a pilot sample may be reissued in an emergency provided it is accompanied by instructions for sampling and for use within six hours after entering the container for sampling;

(3) The blood has been stored continuously at 1 to 6 °C. and shipped between 1 and 10 °C;

(4) The blood is held for observation until a significant inspection consistent with the requirements of §640.5(e) can be made.

(f) *Issue prior to determination of test results.* Notwithstanding the provisions of §610.1 of this chapter, blood may be

issued by the manufacturer on the request of a physician, hospital, or other medical facility before results of all tests prescribed in §640.5, the test for hepatitis B surface antigen prescribed in §610.40(a) of this chapter, and a test for antibody to Human Immunodeficiency Virus (HIV) prescribed in §610.45(a) of this chapter have been completed, where such issue is essential to allow time for transportation to ensure arrival of the blood by the time it is needed for transfusion: *Provided,* That (1) the blood is shipped directly to such physician or medical facility, (2) the records of the manufacturer contain a full explanation of the need for such issue, and (3) the label on each container of such blood bears the information required by §606.121(h) of this chapter.

(Information collection requirements approved by the Office of Management and Budget under number 0910–0227)

[38 FR 32089, Nov. 20, 1973, as amended at 41 FR 4015, Jan. 28, 1976; 42 FR 59878, Nov. 22, 1977; 43 FR 34460, Aug. 4, 1978; 49 FR 15187, Apr. 18, 1984; 49 FR 23834, June 8, 1984; 50 FR 4138, Jan. 29, 1985; 53 FR 116, Jan. 5, 1988; 55 FR 11013, Mar. 26, 1990]

§640.3 Suitability of donor.

(a) *Method of determining.* The suitability of a donor as a source of Whole Blood shall be determined by a qualified physician or by persons under his supervision and trained in determining suitability. Such determination shall be made on the day of collection from the donor by means of medical history, a test for hemoglobin level, and such physical examination as appears necessary to a physician who shall be present on the premises when examinations are made, except that the suitability of donors may be determined when a physician is not present on the premises, provided the establishment (1) maintains on the premises, and files with the Center for Biologics Evaluation and Research, a manual of standard procedures and methods, approved by the Director of the Center for Biologics Evaluation and Research, that shall be followed by employees who determine suitability of donors, and (2) maintains records indicating the name and qualifications of the person immediately in charge of the employees who determine the suitability of donors when a physician is not present on the premises.

(b) *Qualifications of donor; general.* Except as provided in paragraph (f), a person may not serve as a source of Whole Blood more than once in 8 weeks. In addition, donors shall be in good health, as indicated in part by:

(1) Normal temperature;

(2) Demonstration that systolic and diastolic blood pressures are within normal limits, unless the examining physician is satisfied that an individual with blood pressures outside these limits is an otherwise qualified donor under the provisions of this section;

(3) A blood hemoglobin level which shall be demonstrated to be no less than 12.5 gm. of hemoglobin per 100 ml. of blood;

(4) Freedom from acute respiratory diseases;

(5) Freedom from any infectious skin disease at the site of phlebotomy and from any such disease generalized to such an extent as to create a risk of contamination of the blood;

(6) Freedom from any disease transmissible by blood transfusion, insofar as can be determined by history and examinations indicated above; and

(7) Freedom of the arms and forearms from skin punctures or scars indicative of addiction to self-injected narcotics.

(c) *Additional qualifications of donor; viral hepatitis.* No individual shall be used as a source of Whole Blood if he has—

(1) A history of viral hepatitis;

(2) A history of close contact within six months of donation with an individual having viral hepatitis;

(3) A history of having received within six months human blood, or any derivative of human blood which the Food and Drug Administration has advised the licensed establishment is a possible source of viral hepatitis.

(d) *Therapeutic bleedings.* Blood withdrawn in order to promote the health of a donor otherwise qualified under the provisions of this section, shall not be used as a source of Whole Blood unless the container label conspicuously indicates the donor's disease that necessitated withdrawal of blood.

(e) *Immunized donors.* Blood withdrawn from donors known to have been

immunized to human blood cell antigens shall not be used for Whole Blood unless the container label conspicuously indicates such information.

(f) *Qualifications; donations within less than 8 weeks.* A person may serve as a source of Whole Blood more than once in 8 weeks only if at the time of donation the person is examined and certified by a physician to be in good health, as indicated in part in paragraph (b) of this section.

[38 FR 32089, Nov. 20, 1973, as amended at 49 FR 23834, June 8, 1984; 50 FR 4138, Jan. 29, 1985; 51 FR 15611, Apr. 25, 1986; 55 FR 11013, Mar. 26, 1990]

§ 640.4 Collection of the blood.

(a) *Supervision.* Blood shall be drawn from the donor by a qualified physician or under his supervision by assistants trained in the procedure. A physician shall be present on the premises when blood is being collected, except that blood may be collected when a physician is not present on the premises, provided the establishment (1) maintains on the premises, and files with the Center for Biologics Evaluation and Research, a manual of standard procedures and methods, approved by the Director of the Center for Biologics Evaluation and Research, that shall be followed by employees who collect blood, and (2) maintains records indicating the name and qualifications of the person immediately in charge of the employees who collect blood when a physician is not present on the premises.

(b) *The donor clinic.* The pertinent requirements of §§ 600.10 and 600.11 of this chapter shall apply at both the licensed establishment and at any other place where the bleeding is performed.

(c) *Blood containers.* Blood containers and donor sets shall be pyrogen–free, sterile and identified by lot number. The amount of anticoagulant required for the quantity of blood to be collected shall be in the blood container when it is sterilized. In addition, all container and donor set surfaces that come in contact with blood used in the processing of Heparin Whole Blood shall be water repellent.

(d) *The anticoagulant solution.* The anticoagulant solution shall be sterile and pyrogen-free. One of the following formulae shall be used in the indicated volumes:

(1) *Anticoagulant citrate dextrose solution (ACD).*

	Solution A	Solution B
Tri-sodium citrate ($Na_3C_6H_5O_7 \cdot 2H_2O$).	22.0 gm ...	13.2 gm.
Citric acid ($C_6H_8O_7 \cdot H_2O$)	8.0 gm	4.8 gm.
Dextrose ($C_6H_{12}O_6 \cdot H_2O$)	24.5 gm ...	14.7 gm.
Water for injection (U.S.P.) to make.	1,000 ml ..	1,000 ml.
Volume per 100 ml. blood	15 ml	25 ml.

(2) *Anticoagulant heparin solution.*

Heparin sodium (U.S.P.)	75,000 units.
Sodium chloride injection (U.S.P.) to make.	1,000 ml.
Volume per 100 ml. blood	6 ml.

A buffer to maintain stability shall be added, if necessary.

(3) *Anticoagulant citrate phosphate dextrose solution (CPD).*

Tri-sodium citrate ($Na_3C_6H_5O_7 \cdot 2H_2O$) ..	26.3 gm.
Citric acid ($C_6H_8O_7 \cdot H_2O$)	3.27 gm.
Dextrose ($C_6H_{12}O_6 \cdot H_2O$)	25.5 gm.
Monobasic sodium phosphate ($NaH_2PO_4 \cdot H_2O$).	2.22 gm.
Water for injection (U.S.P.) to make	1,000 ml.
Volume per 100 ml. blood	14 ml.

(4) *Anticoagulant citrate phosphate dextrose adenine solution (CPDA–1).*

Tri-sodium citrate ($Na_3C_6H_5O_7 \cdot 2H_2O$) ..	26.3 gm.
Citric acid ($C_6H_8O_7 \cdot H_2O$)	3.27 gm.
Dextrose ($C_6H_{12}O_6 \cdot H_2O$)	31.9 gm.
Monobasic sodium phosphate ($NaH_2PO_4 \cdot H_2O$).	2.22 gm.
Adenine ($C_5H_5N_5$)	0.275 gm.
Water for injection (U.S.P.) to make	1,000 ml.
Volume per 100 ml blood	14 ml.

(e) *Donor identification.* Each unit of blood shall be so marked or identified by number or other symbol as to relate it to the individual donor whose identity shall be established to the extent necessary for compliance with § 640.3.

(f) *Prevention of contamination of the blood.* The skin of the donor at the site of phlebotomy shall be prepared thoroughly and carefully by a method that gives maximum assurance of a sterile container of blood. The blood shall be collected by aseptic methods in a sterile system which may be closed or may be vented if the vent protects the blood against contamination.

(g) *Pilot samples for laboratory tests.* Pilot samples for laboratory tests shall meet the following standards:

(1) One or more pilot samples shall be provided with each unit of blood when

issued or reissued except as provided in §640.2(e)(2) and all pilot samples shall be from the donor who is the source of the unit of blood.

(2) All samples for laboratory tests performed by the manufacturer and all pilot samples accompanying a unit of blood shall be collected at the time of filling the final container by the person who collects the unit of blood.

(3) All containers for all samples shall bear the donor's identification before collecting the samples.

(4) All containers for pilot samples accompanying a unit of blood shall be attached to the whole blood container before blood collection, in a tamperproof manner that will conspicuously indicate removal and reattachment.

(5) When CPDA–1 is used, pilot samples for compatibility testing shall contain blood mixed with CPDA–1.

(h) *Phlebotomy for Heparin Whole Blood.* Heparin Whole Blood shall be collected with minimal damage to and minimal manipulation of the donor's tissue, and with a single, uninterrupted, freeflowing venipuncture.

(i) *Storage.* Immediately after collection, unless the blood is to be used as a source for Platelets, it shall be placed in storage at a temperature between 1 and 6 °C unless it must be transported from the donor clinic to the processing laboratory. In the latter case, the blood shall be placed in temporary storage having sufficient refrigeration capacity to cool the blood continuously toward a range between 1 and 6 °C until it arrives at the processing laboratory, where it shall be stored at a temperature between 1 and 6 °C. Blood from which Platelets is to be prepared shall be held in an environment maintained at a temperature range 20 to 24 °C until the platelets are separated. The red blood cells shall be placed in storage at a temperature between 1 and 6 °C immediately after the platelets are separated.

[38 FR 32089, Nov. 20, 1973, as amended at 42 FR 59878, Nov. 22, 1977; 43 FR 34460, Aug. 4, 1978; 49 FR 23834, June 8, 1984; 50 FR 4138, Jan. 29, 1985; 55 FR 11013, Mar. 26, 1990]

§640.5 Testing the blood.

All laboratory tests shall be made on a pilot sample specimen of blood taken from the donor at the time of collecting the unit of blood, and these tests shall include the following:

(a) *Serological test for syphilis.* Whole Blood shall be negative to a serological test for syphilis.

(b) *Determination of blood group.* Each container of Whole Blood shall be classified as to ABO blood group. At least two blood group tests shall be made and the unit shall not be issued until grouping tests by different methods or with different lots of antiserums are in agreement. Only those Anti-A and Anti-B Blood Grouping Reagents licensed under, or that otherwise meet the requirements of, the regulations of this subchapter shall be used, and the technique used shall be that for which the serum is specifically designed to be effective.

(c) *Determination of the Rh factors.* Each container of Whole Blood shall be classified as to Rh type on the basis of tests done on the pilot sample. The label shall indicate the extent of typing and the results of all tests performed. If the test, using Anti-D Blood Grouping Reagent, is positive, the container may be labeled ''Rh Positive''. If this test is negative, the results shall be confirmed by further testing which may include tests for the Rh_o variant (D^u) and for other Rh–Hr factors. Blood maybe labeled ''Rh Negative'' if negative to tests for the Rh_o (D) and Rh_o variant (D^u) factors. If the test using Anti-D Blood Grouping Reagent is negative, but not tested for the Rh_o variant (D^u), the label must indicate that this test was not done. Only Anti-Rh Blood Grouping Reagents licensed under, or that otherwise meet the requirements of, the regulations of this subchapter shall be used, and the technique used shall be that for which the serum is specifically designed to be effective.

(d) *Sterility test.* Whole Blood intended for transfusion shall not be tested for sterility by a method that entails entering the final container before the blood is used for transfusion.

(e) *Inspection.* Whole Blood shall be inspected visually during storage and immediately prior to issue. If the color or physical appearance is abnormal or there is any indication or suspicion of microbial contamination the unit of

Whole Blood shall not be issued for transfusion.

(f) *Test for antibody to HIV.* Whole Blood shall be tested for antibody to HIV as prescribed in §610.45 of this chapter.

[38 FR 32089, Nov. 20, 1973, as amended at 50 FR 4138, Jan. 29, 1985; 53 FR 117, Jan. 5, 1988; 53 FR 12764, Apr. 19, 1988]

§ 640.6 Modifications of Whole Blood.

Upon approval by the Director, Center for Biologics Evaluation and Research, of a supplement to the product license application for Whole Blood a manufacturer may prepare Whole Blood from which the antihemophilic factor has been removed, provided the Whole Blood meets the applicable requirements of this subchapter and the following conditions are met:

(a) The antihemophilic factor shall be removed in accordance with paragraphs (a), (b), and (c) of §640.52.

(b) Although the closed system between the red blood cells and plasma shall be maintained, the red blood cells shall be maintained between 1 and 6° C at all times, including that time when the plasma is being frozen for removal of the antihemophilic factor.

(c) If containers for pilot samples are detached from the blood container during removal of the antihemophilic factor the pilot samples shall be reattached to the unit of Whole Blood Cryoprecipitate Removed as soon as the plasma is returned to the red blood cells. The reattachment of the pilot samples shall be in a tamperproof manner that will conspicuously indicate removal and reattachment.

[38 FR 32089, Nov. 20, 1973, as amended at 49 FR 23834, June 8, 1984; 50 FR 4138, Jan. 29, 1985; 55 FR 11013, Mar. 26, 1990; 59 FR 49351, Sept. 28, 1994]

Subpart B—Red Blood Cells

§ 640.10 Red Blood Cells.

The proper name of this product shall be Red Blood Cells. The product is defined as red blood cells remaining after separating plasma from human blood.

[38 FR 32089, Nov. 20, 1973, as amended at 50 FR 4138, Jan. 29, 1985]

§ 640.11 General requirements.

(a) *Storage.* Immediately after processing, the Red Blood Cells shall be placed in storage and maintained at a temperature between 1 and 6 °C.

(b) *Inspection.* The product shall be inspected immediately after separation of the plasma, periodically during storage, and at the time of issue. The product shall not be issued if there is any abnormality in color or physical appearance or if there is any indication of microbial contamination.

[38 FR 32089, Nov. 20, 1973, as amended at 41 FR 18292, May 3, 1976; 42 FR 59878, Nov. 11, 1977; 50 FR 4139, Jan. 29, 1985]

§ 640.12 Suitability of donor.

The source blood for Red Blood Cells shall be obtained from a donor who meets the criteria for donor suitability prescribed in §640.3.

[38 FR 32089, Nov. 20, 1973, as amended at 50 FR 4139, Jan. 29, 1985]

§ 640.13 Collection of the blood.

(a) The source blood shall be collected as prescribed in §640.4, except that paragraphs (d)(2), and (g), and (h) shall not apply.

(b) Source blood may also be derived from Whole Blood manufactured in accordance with applicable provisions of this subchapter.

[38 FR 32089, Nov. 20, 1973, as amended at 50 FR 4139, Jan. 29, 1985]

§ 640.14 Testing the blood.

Blood from which Red Blood Cells are prepared shall be tested as prescribed in §§610.40 and 610.45 of this chapter and §640.5 (a), (b), and (c).

[53 FR 117, Jan. 5, 1988]

§ 640.15 Pilot samples.

Pilot samples collected in integral tubing or in separate pilot tubes shall meet the following standards:

(a) One or more pilot samples of either the original blood or of the Red Blood Cells being processed shall be provided with each unit of Red Blood Cells when issued or reissued.

(b) Before they are filled, all pilot sample tubes shall be marked or identified so as to relate them to the donor of that unit of red cells.

(c) Before the final container is filled or at the time the final product is prepared, the pilot sample tubes to accompany a unit of cells shall be attached securely to the final container in a tamper proof manner that will conspicuously indicate removal and reattachment.

(d) All pilot sample tubes accompanying a unit of Red Blood Cells shall be filled at the time the blood is collected or at the time the final product is prepared, in each instance by the person who performs the collection or preparation.

[38 FR 32089, Nov. 20, 1973, as amended at 50 FR 4139, Jan. 29, 1985]

§640.16 Processing.

(a) *Separation.* Within 21 days from date of blood collection (within 35 days from date of blood collection when CPDA–1 solution is used as the anticoagulant), Red Blood Cells may be prepared either by centrifugation done in a manner that will not tend to increase the temperature of the blood or by normal undisturbed sedimentation. A portion of the plasma sufficient to insure optimal cell preservation shall be left with the red cells except when a cryoprotective substance is added for prolonged storage.

(b) *Sterile system.* All surfaces that come in contact with the red cells shall be sterile and pyrogen-free. If an open system is used, that is, where the transfer container is not integrally attached to the blood container, and the blood container is entered after blood collection, the plasma shall be separated from the red blood cells with positive pressure maintained on the original container until completely sealed. If the method of separation involves a vented system, that is, when an airway must be inserted in the container for withdrawal of the plasma, the airway and vent shall be sterile and constructed so as to exclude microorganisms and maintain a sterile system.

(c) *Final containers.* Final containers used for Red Blood Cells shall be the original blood containers unless the method of processing requires a different container. The final container shall meet the requirements for blood containers prescribed in §640.2(c). At the time of filing, if a different container is used, it shall be marked or identified by number or other symbol so as to relate it to the donor of that unit of red cells.

[38 FR 32089, Nov. 20, 1973, as amended at 43 FR 34460, Aug. 4, 1978; 50 FR 4139, Jan. 29, 1985]

§640.17 Modifications for specific products.

Red Blood Cells Frozen: A cryophylactic substance may be added to the Red Blood Cells for extended manufacturers' storage at −65° C. or colder, provided the manufacturer submits data considered by the Director, Center for Biologics Evaluation and Research, as adequately demonstrating through in vivo cell survival and other appropriate tests that the addition of the substance, the materials used and the processing methods results in a final product that meets the required standards of safety, purity, and potency for Red Blood Cells, and that the frozen product will maintain those properties for the prescribed dating period. Section 640.11 (a) and (b) do not apply while a cryophylactic substance is present.

[38 FR 32089, Nov. 20, 1973, as amended at 41 FR 18292, May 3, 1976; 49 FR 23834, June 8, 1984; 50 FR 4139, Jan. 29, 1985; 55 FR 11013, Mar. 26, 1990]

Subpart C—Platelets

§640.20 Platelets.

(a) *Proper name and definition.* The proper name of this product shall be Platelets. The product is defined as platelets collected from one unit of blood and resuspended in an appropriate volume of original plasma, as prescribed in §640.24(d).

(b) *Source.* The source material for Platelets shall be plasma which may be obtained by whole blood collection, by plasmapheresis, or by plateletpheresis.

[40 FR 4304, Jan. 29, 1975, as amended at 47 FR 49021, Oct. 29, 1982; 50 FR 4139, Jan. 29, 1985]

§640.21 Suitability of donors.

(a) Whole blood donors shall meet the criteria for suitability prescribed in §640.3.

(b) Plasmapheresis donors shall meet the criteria for suitability prescribed in § 640.63, excluding the phrase ''other than malaria'' in paragraph (c)(9). Informed consent shall be required as prescribed in § 640.61.

(c) Plateletpheresis donors shall meet criteria for suitability as described in a license application or a supplement to the product license, and must have the written approval of the Director, Center for Biologics Evaluation and Research, Food and Drug Administration.

[40 FR 4304, Jan. 29, 1975, as amended at 49 FR 23834, June 8, 1984; 55 FR 11013, Mar. 26, 1990; 59 FR 49351, Sept. 28, 1994]

§ 640.22 Collection of source material.

(a) Whole blood used as the source of Platelets shall be collected as prescribed in § 640.4, except that paragraphs (d)(2) and (h) shall not apply.

(b) If plasmapheresis is used, the procedure for collection shall be prescribed in §§ 640.62, 640.64 (except paragraph (c)(3)), and 640.65.

(c) If plateletpheresis is used, the procedure for collection shall be as described in a license application or a supplement to a product license, and must have the written approval of the Director, Center for Biologics Evaluation and Research, Food and Drug Administration.

(d) The phlebotomy shall be performed by a single uninterrupted venipuncture with minimal damage to, and minimal manipulation of, the donor's tissue.

[40 FR 4304, Jan. 29, 1975, as amended at 45 FR 27927, Apr. 25, 1980; 49 FR 23834, June 8, 1984; 50 FR 4139, Jan. 29, 1985; 55 FR 11013, Mar. 26, 1990; 59 FR 49351, Sept. 28, 1994]

§ 640.23 Testing the blood.

(a) Blood from which plasma is separated for the preparation of Platelets shall be tested as prescribed in §§ 610.40 and 610.45 of this chapter and § 640.5 (a), (b), and (c).

(b) The tests shall be performed on a sample of blood collected at the time of collecting the source blood, and such sample container shall be labeled with the donor's number before the container is filled.

[40 FR 4304, Jan. 29, 1975, as amended at 50 FR 4139, Jan. 29, 1985; 53 FR 117, Jan. 5, 1988]

§ 640.24 Processing.

(a) Separation of plasma and platelets and resuspension of the platelets shall be in a closed system. Platelets shall not be pooled during processing.

(b) Immediately after collection, the whole blood or plasma shall be held in storage between 20 to 24 °C, unless it must be transported from the donor clinic to the processing laboratory. During such transport, all reasonable methods shall be used to maintain the temperature as close as possible to a range between 20 and 24 °C until it arrives at the processing laboratory where it shall be held between 20 and 24 °C until the platelets are separated. The platelet concentrate shall be separated within 4 hours after the collection of the unit of whole blood or plasma.

(c) The time and speed of centrifugation must have been demonstrated to produce an unclumped product, without visible hemolysis, that yields a count of not less than 5.5×10^{10} platelets per unit in at least 75 percent of the units tested.

(d) The volume of original plasma used for resuspension of the platelets shall be determined by the maintenance of a pH of not less than 6.0 during the storage period. The pH shall be measured on a sample of platelets which has been stored for the maximum dating period at the selected storage temperature. One of the following storage temperatures shall be used continuously:

(1) 20 to 24 °C.

(2) 1 to 6 °C.

(e) Final containers used for Platelets shall be colorless and transparent to permit visual inspection of the contents; any closure shall maintain a hermetic seal and prevent contamination of the contents. The container material shall not interact with the contents, under the customary conditions of storage and use, in such a manner as to have an adverse effect upon the safety, purity, potency, or efficacy of the product. At the time of filling, the final container shall be marked or identified

by number so as to relate it to the donor.

[40 FR 4304, Jan. 29, 1975, as amended at 42 FR 10983, Feb. 25, 1977; 47 FR 49021, Oct. 29, 1982; 50 FR 4139, Jan. 29, 1985]

§ 640.25 General requirements.

(a) *Storage.* Immediately after resuspension, Platelets shall be placed in storage at the selected temperature range. If stored at 20 to 24 °C, a continuous gentle agitation of the platelet concentrate shall be maintained throughout the storage period. Agitation is optional if stored at a temperature between 1 and 6 °C.

(b) *Quality control testing.* Each month four units prepared from different donors shall be tested at the end of the storage period as follows:

(1) Platelet count.

(2) pH of not less than 6.0 measured at the storage temperature of the unit.

(3) Measurement of actual plasma volume.

(4) If the results of the quality control testing indicate that the product does not meet the prescribed requirements, immediate corrective action shall be taken and a record maintained of such action.

(c) *Manufacturing responsibility.* All manufacturing of Platelets shall be performed at the same licensed establishment, except that the quality control testing under paragraph (b) of this section may be performed by a clinical laboratory which meets the standards of the Clinical Laboratories Improvement Act of 1967 (CLIA) (42 U.S.C. 263a) and is qualified to perform platelet counts. Such arrangements must be approved by the Director, Center for Biologics Evaluation and Research, Food and Drug Administration. Such testing shall not be considered as divided manufacturing, as described in §610.63 of this chapter, provided the following conditions are met:

(1) The results of each test are received within 10 days of the preparation of the platelet concentrate, and are maintained by the establishment licensed for Platelets so that they may be reviewed by an authorized representative of the Food and Drug Administration.

(2) The licensed Platelets manufacturer has obtained a written agreement that the testing laboratory will permit an authorized representative of the Food and Drug Administration to inspect its testing procedures and facilities during reasonable business hours.

(3) The testing laboratory will participate in any proficiency testing programs undertaken by the Center for Biologics Evaluation and Research, Food and Drug Administration.

[40 FR 4304, Jan. 29, 1975, as amended at 47 FR 49021, Oct. 29, 1982; 49 FR 23834, June 8, 1984; 50 FR 4139, Jan. 29, 1985; 55 FR 11013, Mar. 26, 1990]

§ 640.27 Emergency provisions.

The use of the plateletpheresis procedure to obtain a product for a specific recipient may be at variance with §§640.21(c) and 640.22(c): *Provided,* That: (a) A licensed physician has determined that the recipient must be transfused with the platelets from a specific donor, and (b) the plateletpheresis procedure is performed under the supervision of a qualified licensed physician who is aware of the health status of the donor and the physician has certified in writing that the donor's health permits plateletpheresis.

[40 FR 53544, Nov. 18, 1975]

Subpart D—Plasma

§ 640.30 Plasma.

(a) *Proper name and definition.* The proper name of this product shall be Plasma. The product is defined as the fluid portion of one unit of human blood intended for intravenous use which in a closed system, has been collected, stabilized against clotting, and separated from the red blood cells.

(b) *Source.* (1) Plasma shall be obtained by separating plasma from blood collected from blood donors or by plasmapheresis.

(2) Plasma may be obtained from a unit of Whole Blood collected by another licensed establishment.

[42 FR 59878, Nov. 22, 1977; 48 FR 13026, Mar. 29, 1983, as amended at 50 FR 4139, Jan. 29, 1985]

§ 640.31 Suitability of donors.

(a) Whole blood donors shall meet the criteria for donor suitability prescribed in § 640.3.

(b) Plasmapheresis donors shall meet the criteria for donor suitability prescribed in § 640.63, excluding the phrase ''other than malaria'' in paragraph (c)(9) of that section. Informed consent shall be required as prescribed in § 640.61.

(c) Donors shall not be suitable if they are known to have been immunized within the past 6 months by injection with human red blood cells.

[42 FR 59878, Nov. 22, 1977]

§ 640.32 Collection of source material.

(a) Whole blood shall be collected, transported, and stored as prescribed in § 640.4, except that paragraphs (d)(2) and (h) of that section shall not apply. When whole blood is intended for Plasma, Fresh Frozen Plasma, and Liquid Plasma, it shall be maintained at a temperature between 1 and 6 °C until the plasma is removed. Whole blood intended for Platelet Rich Plasma, shall be maintained as prescribed in § 640.24 until the plasma is removed. The red blood cells shall be placed in storage at a temperature between 1 and 6 °C immediately after the plasma is separated.

(b) Plasma obtained by plasmapheresis shall be collected as prescribed in §§ 640.62, 640.64 (except that paragraph (c)(3) of § 640.64 shall not apply), and § 640.65.

[42 FR 59878, Nov. 22, 1977, as amended at 45 FR 27927, Apr. 25, 1980; 50 FR 4139, Jan. 29, 1985]

§ 640.33 Testing the blood.

(a) Blood from which plasma is separated shall be tested as prescribed in §§ 610.40 and 610.45 of this chapter and § 640.5 (a), (b), and (c).

(b) Manufacturers of Plasma collected by plasmapheresis shall have testing and recordkeeping responsibilities equivalent to those prescribed in §§ 640.71 and 640.72.

[42 FR 59878, Nov. 22, 1977, as amended at 44 FR 17658, Mar. 23, 1979; 50 FR 4139, Jan. 29, 1985; 53 FR 117, Jan. 5, 1988]

§ 640.34 Processing.

(a) *Plasma.* Plasma shall be separated from the red blood cells within 26 days after phlebotomy (within 40 days after phlebotomy when CPDA–1 solution is used as the anticoagulant), and shall be stored at −18 °C or colder within 6 hours after transfer to the final container, unless the product is to be stored as Liquid Plasma .

(b) *Fresh Frozen Plasma.* Fresh Frozen Plasma shall be prepared from blood collected by a single uninterrupted venipuncture with minimal damage to and minimal manipulation of the donor's tissue. The plasma shall be separated from the red blood cells, frozen solid within 6 hours after phlebotomy, and stored at −18 °C or colder.

(c) *Liquid Plasma.* Liquid Plasma shall be separated from the red blood cells within 26 days after phlebotomy (within 40 days after phlebotomy when CPDA–1 solution is used as the anticoagulant) and shall be stored at a temperature of 1 to 6 °C within 4 hours after filling the final container.

(d) *Platelet Rich Plasma.* Platelet Rich Plasma shall be prepared from blood collected by a single uninterrupted venipuncture with minimal damage to and manipulation of the donor's tissue. The plasma shall be separated from the red blood cells by centrifugation within 4 hours after phlebotomy. The time and speed of centrifugation shall have been shown to produce a product with at least 250,000 platelets per microliter. The plasma shall be stored at a temperature between 20 to 24 °C or between 1 and 6 °C, immediately after filling the final container. A gentle and continuous agitation of the product shall be maintained throughout the storage period, if stored at a temperature of 20 to 24 °C.

(e) *Modifications of Plasma.* It is possible to separate Platelets and/or Cryoprecipitated AHF from Plasma. When these components are to be separated, the plasma shall be collected as described in § 640.32 for Plasma.

(1) Platelets shall be separated as prescribed in subpart C of part 640, prior to freezing the plasma. The remaining plasma may be labeled as Fresh Frozen Plasma, if frozen solid within 6 hours after phlebotomy.

(2) Cryoprecipitated AHF shall be removed as prescribed in Subpart F of part 640. The remaining plasma may be labeled Plasma.

(3) Plasma remaining after both Platelets and Cryoprecipitated AHF have been removed may be labeled Plasma.

(f) *The final container.* (1) The final container shall have no color added to the plastic and shall be transparent to permit visual inspection of the contents; any closure shall maintain a hermetic seal and prevent contamination of the contents.

(2) The final container material shall not interact with the contents, under the customary conditions of storage and use, in such a manner as to have an adverse effect upon the safety, purity, potency, and effectiveness of the product.

(3) Prior to filling, the final container shall be identified by number so as to relate it to the donor.

(g) *The final product.* (1) The final product shall be inspected immediately after separation of the plasma and shall not be issued for transfusion if there is (i) any abnormality in color or physical appearance, or (ii) any indication of contamination.

(2) With the exception of Platelet Rich Plasma and Liquid Plasma, the final product shall be stored in a manner that will show evidence of thawing and shall not be issued if there is any evidence of thawing of the product during storage or breakage of the container.

(3) No preservative shall be added to the final product.

[42 FR 59878, Nov. 22, 1977, as amended at 43 FR 34460, Aug. 4 1978; 48 FR 13026, Mar. 29, 1983; 50 FR 4139, Jan. 29, 1985]

Subpart E [Reserved]

Subpart F—Cryoprecipitate

§ 640.50 Cryoprecipitated AHF.

(a) *Proper name and definition.* The proper name of this product shall be Cryoprecipitated AHF. The product is defined as a preparation of antihemophilic factor, which is obtained from a single unit of plasma collected and processed in a closed system.

(b) *Source.* The source material for Cryoprecipitated AHF shall be plasma which may be obtained by whole blood collection or by plasmapheresis.

[42 FR 21774, Apr. 29, 1977; 48 FR 13026, Mar. 29, 1983; as amended at 50 FR 4139, Jan. 29, 1985]

§ 640.51 Suitability of donors.

(a) Whole blood donors shall meet the criteria for suitability prescribed in § 640.3.

(b) Plasmaphersis donors shall meet the criteria for suitability prescribed in § 640.63, excluding the phrase ''other than malaria'' in paragraph (c) (9) of that section. Informed consent shall be required as prescribed in § 640.61.

(c) Donors shall not be suitable if they are known to have been immunized by injection with human red blood cells within the last 6 months.

[42 FR 21774, Apr. 29, 1977]

§ 640.52 Collection of source material.

(a) Whole blood used as a source of Cryoprecipitated AHF shall be collected as prescribed in § 640.4, except that paragraphs (d) (2), (g), and (h) of that section shall not apply. Whole blood from which both Platelets and Cryoprecipitated AHF is derived shall be maintained as required under § 640.24 until the platelets are removed.

(b) If plasmapheresis is used, the procedure for collection shall be as prescribed in §§ 640.62, 640.64 (except that paragraph (c)(3) of that section shall not apply), and 640.65.

[42 FR 21774, Apr. 29, 1977, as amended by 50 FR 4139, Jan. 29, 1985]

§ 640.53 Testing the blood.

(a) Blood from which plasma is separated for the preparation of Cryoprecipitated AHF shall be tested as prescribed in §§ 610.40 and 610.45 of this chapter and § 640.5 (a), (b), and (c).

(b) The tests shall be performed on a sample of blood collected at the time of collecting the source blood, and such sample container shall be labeled with the donor's number before the container is filled.

(c) Manufacturers of Cryoprecipitated AHF obtained from

plasma collected by plasmapheresis shall have testing and record-keeping responsibilities equivalent to those prescribed in §§ 640.71 and 640.72.

[42 FR 21774, Apr. 29, 1977, as amended at 42 FR 37546, July 22, 1977; 42 FR 43063, Aug. 26, 1977; 50 FR 4139, Jan. 29, 1985; 53 FR 117, Jan. 5, 1988]

§ 640.54 Processing.

(a) *Processing the plasma.* (1) The plasma shall be separated from the red blood cells by centrifugation to obtain essentially cell-free plasma.

(2) The plasma shall be frozen solid within 6 hours after blood collection. A combination of dry ice and organic solvent may be used for freezing: *Provided,* That the procedure has been shown not to cause the solvent to penetrate the container or leach plasticizer from the container into the plasma.

(3) Immediately after separation and freezing of the plasma, the plasma shall be stored and maintained at −18 °C or colder until thawing of the plasma for further processing to remove the Cryoprecipitated AHF.

(b) *Processing the final product.* (1) The Cryoprecipitated AHF shall be separated from the plasma by a procedure that has been shown to produce an average of no less than 80 units of antihemophilic factor per final container.

(2) No diluent shall be added to the product by the manufacturer prior to freezing.

(3) The final container used for Cryoprecipitated AHF shall be colorless and transparent to permit visual inspection of the contents; any closure shall maintain a hermetic seal and prevent contamination of the contents. The container material shall not interact with the contents under customary conditions of storage and use in such a manner as to have an adverse effect upon the safety, purity, potency and effectiveness of the product. At the time of filling, the final container shall be identified by a number so as to relate it to the donor.

[42 FR 21774, Apr. 29, 1977, as amended at 47 FR 15330, Apr. 9, 1982; 50 FR 4139, Jan. 29, 1985]

§ 640.55 U.S. Standard preparation.

A U.S. Standard Antihemophilic Factor (Factor VIII) preparation may be obtained from the Center for Biologics Evaluation and Research, Food and Drug Administration, for use in the preparation of a working reference to be employed in a quality control potency test of Cryoprecipitated AHF.

[42 FR 21774, Apr. 29, 1977, as amended at 49 FR 23834, June 8, 1984; 50 FR 4140, Jan. 29, 1985; 55 FR 11013, Mar. 26, 1990]

§ 640.56 Quality control test for potency.

(a) Quality control tests for potency of antihemophilic factor shall be conducted each month on at least four representative containers of Cryoprecipitated AHF.

(b) The results of each test are received by the establishment licensed for Cryoprecipitated AHF within 30 days of the preparation of the cryoprecipitated antihemophilic factor and are maintained at that establishment so that they may be reviewed by an authorized representative of the Food and Drug Administration.

(c) The quality control test for potency may be performed by a clinical laboratory which meets the standards of the Clinical Laboratories Improvement Act of 1967 (CLIA) (42 U.S.C. 263a) and is qualified to perform potency tests for antihemophilic factor. Such arrangements must be approved by the Director, Center for Biologics Evaluation and Research, Food and Drug Administration. Such testing shall not be considered as divided manufacturing, as described in § 610.63 of this chapter, provided the following conditions are met:

(1) The establishment licensed for Cryoprecipitated AHF has obtained a written agreement that the testing laboratory will permit an authorized representative of the Food and Drug Administration to inspect its testing procedures and facilities during reasonable business hours.

(2) The testing laboratory will participate in any proficiency testing programs undertaken by the Center for Biologics Evaluation and Research, Food and Drug Administration.

(d) If the average potency level of antihemophilic factor in the containers

tested is less than 80 units of antihemophilic factor per container, immediate corrective actions shall be taken and a record maintained of such action.

[42 FR 21774, Apr. 29, 1977, as amended at 49 FR 23834, June 8, 1984; 50 FR 4140, Jan. 29, 1985; 55 FR 11013, Mar. 26, 1990]

Subpart G—Source Plasma

§ 640.60 Source Plasma.

The proper name of the product shall be Source Plasma. The product is defined as the fluid portion of human blood collected by plasmapheresis and intended as source material for further manufacturing use. The definition excludes single donor plasma products intended for intravenous use.

[41 FR 10768, Mar. 12, 1976, as amended at 50 FR 4140, Jan. 29, 1985]

§ 640.61 Informed consent.

The written consent of a prospective donor shall be obtained after a qualified licensed physician has explained the hazards of the procedure to the prospective donor. The explanation shall include the risks of a hemolytic transfusion reaction if he is given the cells of another donor, and the hazards involved if he is hyperimmunized. The explanation shall consist of such disclosure and be made in such a manner that intelligent and informed consent be given and that a clear opportunity to refuse is presented.

§ 640.62 Medical supervision.

A qualified licensed physician shall be on the premises when donor suitability is being determined, immunizations are being made, whole blood is being collected, and red blood cells are being returned to the donor.

§ 640.63 Suitability of donor.

(a) *Method of determining.* The suitability of a donor for Source Plasma shall be determined by a qualified licensed physician or by persons under his supervision and trained in determining donor suitability. Such determination shall be made on the day of collection from the donor by means of a medical history, tests, and such physical examination as appears necessary to the qualified licensed physician.

(b) *Initial medical examinations.* (1) Each donor shall be examined by a qualified licensed physician on the day of the first donation or no more than 1 week before the first donation and at subsequent intervals of no longer than 1 year.

(2)(i) A donor who is to be immunized for the production of high-titer plasma shall be examined by a qualified licensed physician. The medical examination shall be performed within no more than 1 week before the first immunization injection. The medical examination for plasmapheresis need not be repeated, if the first donation occurs within 3 weeks after the first injection.

(ii) A donor who is an active participant in a plasmapheresis program, and has been examined in accordance with paragraph (b)(1) of this section, need not be reexamined before immunization for the production of high-titer plasma.

(3) Each donor shall be certified to be in good health by the examining physician. The certification of good health shall be on a form supplied by the licensed establishment and shall indicate that the certification applies to the suitability of the individual to be a plasmapheresis donor and, when applicable, an immunized donor.

(c) *Qualification of donor.* Donors shall be in good health on the day of donation, as indicated in part by:

(1) Normal temperature;

(2) Demonstration that systolic and diastolic blood pressures are within normal limits, unless the examining physician is satisfied that an individual with blood pressures outside these limits is an otherwise qualified donor under the provisions of this section;

(3) A blood hemoglobin level of no less than 12.5 grams of hemoglobin per 100 milliliters of blood;

(4) A normal pulse rate;

(5) A total serum protein of no less than 6.0 grams per 100 milliliters of serum;

(6) Weight, which shall be at least 110 pounds;

(7) Freedom from acute respiratory diseases;

(8) Freedom from any infectious skin disease at the site of phlebotomy and

from any such disease generalized to such an extent as to create a risk of contamination of the plasma;

(9) Freedom from any disease, other than malaria, transmissible by blood transfusion, insofar as can be determined by history and examinations indicated in this section;

(10) Freedom of the arms and forearms from skin punctures or scars indicative of addiction to self-injected narcotics;

(11) Freedom from a history of viral hepatitis;

(12) Freedom from a history of close contact within six months of donation with an individual having viral hepatitis;

(13) Freedom from a history of having received, within six months, human blood or any derivative of human blood which the Food and Drug Administration has advised the licensed establishment is a possible source of viral hepatitis, except for specific immunization performed in accordance with § 640.66 of this part.

(d) *General.* Any donor who, in the opinion of the interviewer, appears to be under the influence of any drug, alcohol, or for any reason does not appear to be providing reliable answers to medical history questions, shall not be considered a suitable donor.

(e) *Failure to return red blood cells.* Any donor who has not had the red blood cells returned from a unit of blood collected during a plasmapheresis procedure or who has been a donor of a unit of whole blood shall not be subjected to plasmapheresis for a period of 8 weeks, unless:

(1) The donor has been examined by a qualified licensed physician and certified by the physician to be acceptable for further plasmapheresis before expiration of the 8-week period;

(2) The donor possesses an antibody that is (i) transitory, (ii) of a highly unusual or infrequent specificity, or (iii) of an unusually high titer; and

(3) The special characteristics of the antibody and the need for plasmapheresing the donor are documented.

[38 FR 32089, Nov. 20, 1973, as amended at 41 FR 10768, Mar. 12, 1976; 43 FR 9805, Mar. 10, 1978; 43 FR 12311, Mar. 24, 1978; 46 FR 57480, Nov. 24, 1981; 50 FR 4140, Jan. 29, 1985]

§ 640.64 Collection of blood for Source Plasma.

(a) *Supervision.* All blood for the collection of Source Plasma shall be drawn from the donor by a qualified licensed physician or by persons under his supervision trained in the procedure.

(b) *Blood containers.* Blood containers and donor sets shall be pyrogen-free, sterile and identified by lot number. The amount of anticoagulant required for the quantity of blood to be collected shall be in the blood container when it is sterilized.

(c) *The anticoagulant solution.* The anticoagulant solution shall be sterile and pyrogen-free. One of the following formulas shall be used in the indicated volumes, except that a different formula may be used for plasma for manufacture into noninjectable products if prior written approval is obtained from the Director of the Center for Biologics Evaluation and Research at the time of licensing or in the form of a supplement to the Source Plasma product license.

(1) *Anticoagulant citrate dextrose solution (ACD).*

Tri-sodium citrate ($Na_3C_6H_5O_7 \cdot 2H_2O$)	22.0 grams.
Citric acid ($C_6H_8O_7 \cdot H_2O$)	8.0 grams.
Dextrose ($C_6H_{12}O_6H_2O$)	24.5 grams.
Water for injection (U.S.P.) to make.	1,000 milliliters.
Volume per 100 milliliters blood	15 milliliters.

(2) *Anticoagulant citrate phosphate dextrose solution (CPD).*

Tri-sodium citrate ($Na_3C_6H_5O_7 \cdot 2H_2O$)	26.3 grams.
Citric acid ($C_6H_8O \cdot H_2O$)	3.27 grams.
Dextrose ($C_6H_{12}O_6H_2O$)	25.5 grams.
Monobasic sodium phosphate ($NaH_2PO_4 \cdot H_2O$).	2.22 grams.
Water for injection (U.S.P.) to make.	1,000 milliliters.
Volume per 100 milliliters blood	14 milliliters.

(3) *Anticoagulant sodium citrate solution.*

Tri-sodium citrate ($Na_3C_6H_5O_7 \cdot 2H_2O$)	40 grams.
Water for injection (U.S.P.) to make.	1,000 milliliters.
Volume per 100 milliliters of blood	10 milliliters.

(d) *Donor identification.* Each unit of blood and plasma shall be so marked or identified by number or other symbol so as to relate it directly to the donor.

(e) *Prevention of contamination of the blood and plasma.* The skin of the donor

at the site of phlebotomy shall be prepared thoroughly and carefully by a method that gives maximum assurance of a sterile container of blood. The blood shall be collected, the plasma separated, and the cells returned to the donor by aseptic methods in a sterile system which may be closed, or may be vented if the vent protects the blood cells and plasma against contamination.

[38 FR 32089, Nov. 20, 1973; 39 FR 13632, Apr. 16, 1974, as amended at 41 FR 10768, Mar. 12, 1976; 49 FR 23834, June 8, 1984; 50 FR 4140, Jan. 29, 1985; 55 FR 11013, Mar. 26, 1990; 59 FR 49351, Sept. 28, 1994]

§ 640.65 Plasmapheresis.

(a) *Procedure-general.* The plasmapheresis procedure is a procedure in which, during a single visit to the establishment, blood is removed from a donor, the plasma separated from the formed elements, and at least the red blood cells returned to the donor. This procedure shall be described in detail in the product license application.

(b) *Procedures-specific requirements.* The plasmapheresis procedure shall meet the following requirements:

(1)(i) A sample of blood shall be drawn from each donor on the day of the first medical examination or plasmapheresis, whichever comes first and at least every 4 months thereafter by a qualified licensed physician or by persons under his supervision and trained in such procedure. A serologic test for syphilis, a total plasma or serum protein determination, and a plasma or serum protein electrophoresis or quantitative immuno-diffusion test or an equivalent test to determine immunoglobulin composition of the plasma or serum shall be performed on the sample.

(ii) A repeat donor who does not return for plasmapheresis at the time the 4-month sample is due to be collected may be plasmapheresed on the day he appears: *Provided,* That no longer than 6 months has elapsed since the last sample was collected, and the physician on the premises approves the plasmapheresis procedure and so indicates by signing the donor's record before such procedure is performed. The sample for the 4–month tests shall be collected on the day of the donor's return.

(iii) A repeat donor from whom the plasmapheresis center is unable to obtain a sample for testing as prescribed in paragraph (b)(1)(i) of this section for a total period exceeding 6 months shall be processed as a new donor.

(2)(i) The accumulated laboratory data, including tracings, if any, of the plasma or serum protein electrophoresis pattern, the calculated values of each component, and the collection records shall be reviewed by a qualified licensed physician within 21 days after the sample is drawn to determine whether or not the donor may continue in the program. The review shall be signed by the reviewing physician. If the protein composition is not within normal limits established by the testing laboratory, or if the total protein is less than 6.0 grams per 100 milliliters of samples, the donor shall be removed from the program until these values return to normal.

(ii) A donor with a reactive serologic test for syphilis shall not be plasmapheresed again until the donor's serum is tested and found to be nonreactive to a serologic test for syphilis, except as provided in paragraph (b)(2)(iii) and (iv) of this section.

(iii) A donor whose serum is determined to have a biologic false-positive reaction to a serologic test for syphilis may be plasmapheresed: *Provided,* That the donor's file identifies the serologic test for syphilis and results used to confirm the biologic false-positive reaction and indicates that the physician on the premises has determined the false-positive reaction is not the result of an underlying disorder that would disqualify the donor from participation in the plasmapheresis program. If the serologic test for syphilis is performed at a facility other than the plasmapheresis center, all applicable provisions of § 640.71 shall be met.

(iv) A donor with a reactive serologic test for syphilis may be plasmapheresed only to obtain plasma to be used for further manufacturing into control serum for the serologic test for syphilis: *Provided,* That the physician on the premises approves the donation, the donor's file contains a signed statement from a physician or clinic establishing that treatment for syphilis has been initiated and that

continuance in the plasmapheresis program will not interfere with or jeopardize the treatment of the syphilitic donor.

(3) A donor identification system shall be established that positively identifies each donor and relates such donor directly to his blood and its components as well as to his accumulated records and laboratory data. Such system shall include either a photograph of each donor which shall be used on each visit to confirm the donor's identity, or some other method that provides equal or greater assurance of positively identifying the donor.

(4) The amount of whole blood, not including anticoagulant, removed from a donor during a plasmapheresis procedure or in any 48–hour period shall not exceed 1,000 milliliters unless the donor's weight is 175 pounds or greater, in which case the amount of whole blood, not including anticoagulant, removed from the donor during a plasmapheresis procedure or in any 48–hour period shall not exceed 1,200 milliliters.

(5) The amount of whole blood, not including anticoagulant, removed from a donor within a seven-day period shall not exceed 2,000 milliliters unless the donor's weight is 175 pounds or greater, in which case the amount of whole blood, not including anticoagulant, removed from the donor during a seven-day period shall not exceed 2,400 milliliters.

(6) No more than 500 milliliters of whole blood shall be removed from a donor at one time, unless the donor's weight is 175 pounds or greater, in which case no more than 600 milliliters of whole blood shall be removed from the donor at one time.

(7) The plasma shall be separated from the red blood cells immediately after blood collection. The maximum feasible volume of red blood cells shall be returned to the donor before another unit is collected.

[38 FR 32089, Nov. 20, 1973, as amended at 41 FR 10769, Mar. 12, 1976]

§ 640.66 Immunization of donors.

If specific immunization of a donor is to be performed, the selection and scheduling of the injection of the antigen, and the evaluation of each donor's clinical response, shall be by a qualified licensed physician or physicians. The administration of the antigen may be performed by a licensed physician or a trained person under his supervision. Any material used for immunization shall be either a product licensed under section 351 of the Public Health Service Act for such purpose or one specifically approved by the Director, Center for Biologics Evaluation and Research, Food and Drug Administration. Immunization procedures shall be on file at each plasmapheresis center where immunizations are performed.

[38 FR 32089, Nov. 20, 1973, as amended at 49 FR 23834, June 8, 1984; 55 FR 11013, Mar. 26, 1990]

§ 640.67 Laboratory tests.

(a) *Hepatitis B surface antigen.* Each unit of Source Plasma shall be nonreactive to a test for hepatitis B surface antigen as prescribed in §§ 610.40 and 610.41 of this chapter, except insofar as permitted in § 610.40(d)(1) and (d)(2) of this chapter.

(b) *Antibody to HIV.* Each unit of Source Plasma shall be negative by a test for antibody to HIV as prescribed in § 610.45 of this chapter, except as provided in § 610.45(c) of this chapter.

[53 FR 117, Jan. 5, 1988, as amended at 57 FR 10814, Mar. 31, 1992]

§ 640.68 Processing.

(a) *Sterile system.* All administration and transfer sets inserted into blood containers used for processing Source Plasma intended for manufacturing into injectable or noninjectable products and all interior surfaces of plasma containers used for processing Source Plasma intended for manufacturing into injectable products shall be sterile, pyrogen-free, nontoxic, and compatible with the contents under normal conditions of use. Only Sodium Chloride Injection USP shall be used as a red blood cell diluent. If the method of separation of the plasma intended for injectable products involves a system in which an airway must be inserted into the plasma container, the airway shall be sterile and constructed so as to exclude microorganisms and maintain a sterile system.

(b) *Final containers.* Final containers used for Source Plasma, whether integrally attached or separated from the original blood container, shall not be entered prior to issuance for any purpose except for filling with the plasma. Such containers shall be uncolored and hermetically sealed, and shall permit clear visibility of the contents. Final containers and their components shall not interact with the plasma contents under conditions of storage and use so as to alter the safety, quality, purity, or potency of the plasma and shall provide adequate protection against external factors that may cause deterioration or contamination. Prior to filling, the final container shall be marked or identified by number or other symbol which will relate it directly to the donor.

(c) *Preservative.* Source Plasma shall not contain a preservative.

[38 FR 32089, Nov. 20, 1973, as amended at 41 FR 10769, Mar. 12, 1976; 50 FR 4140, Jan. 29, 1985]

§640.69 General requirements.

(a) *Pooling.* Two units of Source Plasma from the same donor may be pooled if such units are collected during one plasmapheresis procedure: *Provided,* That the pooling is done by a procedure that does not introduce a risk of contamination of the red blood cells and, for plasma intended for injectable products, gives maximum assurance of a sterile container of plasma.

(1) The pooling of plasma from two or more donors is not permitted in the manufacture of Source Plasma intended for manufacturing into injectable products.

(2) The pooling of plasma from two or more donors by the manufacturer of Source Plasma intended for manufacturing into noninjectable products is permitted: *Provided,* That the plasma from two or more donors is pooled after the plasma has been removed from the red blood cells, and after the red blood cell containers are sealed.

(b) *Storage.* Immediately after filling, plasma intended for manufacturing into injectable products shall be stored at a temperature not warmer than −20 °C., except for plasma collected as provided in §640.74. Plasma intended for manufacturing into noninjectable products may be stored at temperatures appropriate for the intended use of the final product, provided these temperatures are included in the Source Plasma license application.

(c) *Inspection.* Source Plasma intended for manufacturing into injectable products shall be inspected for evidence of thawing at the time of issuance, except that inspection of individual plasma containers need not be made if the records of continuous monitoring of the storage temperature establish that the temperature remained at −20 °C or colder. If there is evidence that the storage temperature has not been maintained at −20 °C or colder, the plasma may be relabeled and issued as provided in §640.76(a).

(d) *Pilot samples.* If pilot samples are provided, they shall meet the following standards:

(1) Prior to filling, all pilot samples shall be marked or identified so as to relate them directly to the donor of that unit of plasma.

(2) All pilot samples shall be filled at the time the final product is prepared by the person who prepares the final product.

(3) All pilot samples shall be representative of the contents of the final product.

(4) All pilot samples shall be collected in a manner that does not contaminate the contents of the final container.

[38 FR 32089, Nov. 20, 1973, as amended at 41 FR 10769, Mar. 12, 1976; 41 FR 14367, Apr. 5, 1976; 50 FR 4140, Jan. 29, 1985]

§640.70 Labeling.

(a) In addition to the labeling requirements of §610.62 of this chapter, and in lieu of the requirements in §§606.121, 610.60, and 610.61 of this chapter, the following information shall appear on the label affixed to each container of Source Plasma:

(1) The proper name of the product.

(2) The statement ''Caution: For Manufacturing Use Only'' for products intended for further manufacturing into injectable products, or the statement, ''Caution: For Use In Manufacturing Noninjectable Products Only'', for products intended for further manufacturing into noninjectable products. The statement shall follow the proper

name in the same size and type of print as the proper name.

(3) The statement ''Store at −20 °C. or colder'': *Provided*, That where plasma is intended for manufacturing into noninjectable products, this statement may be omitted if replaced by a statement of the temperature appropriate for the final product to be prepared from the plasma.

(4) The total volume or weight of plasma and total quantity and type of anticoagulant used.

(5) The donor number or individual bleed number, or both. If plasma is pooled from two or more donors, either all donor numbers, all bleed numbers, or a pool number that is traceable to each individual unit comprising the pool.

(6) The expiration date of the plasma. If plasma intended for manufacturing into noninjectable products is pooled from two or more donors the expiration date is determined from the collection date of the oldest unit in the pool, and the pooling records shall show the collection date for each unit constituting the pool.

(7) A statement as to whether the plasma was collected from normal donors or from immunized donors. In the case of immunized donors, the label shall state the immunizing antigen.

(8) The test for hepatitis B surface antigen used for the results, or the statement ''Nonreactive for HB_s Ag by FDA required test''.

(9) When plasma collected from a donor is reactive for the serologic test for syphilis, a statement that the plasma is reactive and must be used only for the manufacturing of positive control reagents for the serologic test for syphilis.

(10) Name, address, and license number of the manufacturer.

(11) The statement ''Negative by a test for antibody to HIV'', or equivalent statement.

(b) Source Plasma diverted for Source Plasma Salvaged shall be relabeled ''Source Plasma Salvaged'' as prescribed in §640.76. Immediately following the proper name of the product, the labeling shall conspicuously state as applicable, ''STORAGE TEMPERATURE EXCEEDED −20 °C'' or ''SHIPPING TEMPERATURE EXCEEDED −5 °C''.

[41 FR 10770, Mar. 12, 1976, as amended at 41 FR 27034, July 1, 1976; 41 FR 35062, Aug. 19, 1976; 47 FR 30969, July 16, 1982; 50 FR 4140, Jan. 29, 1985; 50 FR 35471, Aug. 30, 1985; 53 FR 117, Jan. 5, 1988]

§ 640.71 Manufacturing responsibility.

(a) All steps in the manufacture of Source Plasma, including donor examination, blood collection, plasmapheresis, laboratory testing, labeling, storage, and issuing shall be performed by personnel of the establishment licensed to manufacture Source Plasma, except that the following tests may be performed by personnel of an establishment licensed for blood or blood derivatives under section 351(a) of the Public Health Service Act, or by a clinical laboratory that meets the standards of the Clinical Laboratories Improvement Act of 1967 (CLIA) (42 U.S.C. 263a): *Provided*, The establishment or the clinical laboratory is qualified to perform the assigned test(s).

(1) The test for hepatitis B surface antigen.

(2) The total plasma or serum protein and the quantitative test for plasma or serum proteins or for immunoglobulins.

(3) The serologic test for syphilis.

(4) A test for antibody to HIV.

(b) Such testing shall not be considered divided manufacturing, which requires two product licenses for Source Plasma: *Provided*, That

(1) The results of such tests are maintained by the establishment licensed for Source Plasma whereby such results may be reviewed by a licensed physician as required in §640.65(b)(2) and by an authorized representative of the Food and Drug Administration.

(2) The Source Plasma manufacturer has obtained a written agreement that the testing laboratory will permit authorized representatives of the Food and Drug Administration to inspect its testing procedures and facilities during reasonable business hours.

(3) The testing laboratory will participate in any proficiency testing programs undertaken by the Center for

Biologics Evaluation and Research, Food and Drug Administration.

[41 FR 10770, Mar. 12, 1976, as amended at 49 FR 23834, June 8, 1984; 50 FR 4140, Jan. 29, 1985; 53 FR 117, Jan. 5, 1988; 55 FR 11013, Mar. 26, 1990]

§640.72 Records.

(a) In addition to the recordkeeping requirements of this subchapter, the following records shall be maintained:

(1) Documentation compiled every 3 months establishing that the shipping temperature requirements of §600.15 of this title and §640.74(b)(2) are being met for Source Plasma intended for manufacture into injectable products.

(2) For each donor, a separate and complete record of all initial and periodic examinations, tests, laboratory data, interviews, etc., undertaken pursuant to §§640.63, 640.65, 640.66, and 640.67, except that negative test results for hepatitis B surface antigen, negative test results for antibody to HIV, and the volume or weight of plasma withdrawn from a donor need not be kept on the individual donor record: *Provided,* That such information is maintained on the premises of the plasmapheresis center where the donor's plasma has been collected.

(3) The original or a clear copy of the donor's written consent for participation in the plasmapheresis program or for immunization.

(4) The certification of the donor's good health as prescribed in §640.63(b)(3).

(5) If plasma that is reactive to a serologic test for syphilis is issued as prescribed in §640.65(b)(2)(iv), the distribution records shall indicate by number those units that are reactive.

(b) Each donor record must be directly cross-referenced to the unit(s) of Source Plasma associated with the donor.

(c) If a repeat donor is rejected or a donor's plasma is found unsuitable, the donor's record shall contain a full explanation for the rejection.

(d) If a donor has a reaction while on the plasmapheresis premises, or a donor reaction is reported to the center after the donor has left the premises, the donor's record shall contain a full explanation of the reaction, including the measures taken to assist the donor and the outcome of the incident.

(Collection of information requirements approved by the Office of Management and Budget under control number 0910–0227)

[41 FR 10770, Mar. 12, 1976, as amended at 50 FR 4140, Jan. 29, 1985; 53 FR 117, Jan. 5, 1988]

§640.73 Reporting of fatal donor reactions.

If a donor has a fatal reaction which, in any way, may be associated with plasmapheresis the Director of the Center for Biologics Evaluation and Research shall be notified by telephone as soon as possible. If the facility is located outside of the continental United States, notification by cable or telegram shall be acceptable.

[41 FR 10770, Mar. 12, 1976, as amended at 49 FR 23834, June 8, 1984; 55 FR 11013, Mar. 26, 1990]

§640.74 Modification of Source Plasma.

(a) Upon approval by the Director, Center for Biologics Evaluation and Research, Food and Drug Administration, of a supplement to the product license for Source Plasma, a manufacturer may prepare Source Plasma as a liquid product for a licensed blood derivative manufacturer who has indicated a need for a liquid product.

(b) Source Plasma Liquid shall meet all standards of the frozen Source Plasma except:

(1) Source Plasma Liquid shall be stored in nonleachable containers so that the containers and their components will not interact with the plasma contents under conditions of storage and use so as to alter the safety, quality, purity, or potency of the plasma and shall provide adequate protection against external factors that may cause deterioration or contamination.

(2) Source Plasma Liquid shall be shipped, stored and labeled for storage at a temperature of 10 °C. or colder. An exception to the shipping or storage temperature shall be approved by the Director, Center for Biologics Evaluation and Research, Food and Drug Administration, based upon his receipt of substantial evidence to support another temperature. Such evidence may be submitted by either the product licensee of the Source Plasma Liquid or

the manufacturer of the final blood derivative product who has requested the Source Plasma Liquid.

(3) The label for the Source Plasma Liquid shall be easily distinguished from that of the frozen product. Color coding shall not be used for this purpose.

(4) The label affixed to each container of Source Plasma Liquid shall contain, in addition to the information required by §640.70(a) but excluding §640.70(a)(3), the name of the manufacturer of the final blood derivative product for whom it was prepared.

(5) Source Plasma Liquid shall be inspected immediately prior to issuance. If the color or physical appearance is abnormal, or there is any indication or suspicion of microbial contamination, the unit of Source Plasma Liquid shall not be issued.

[38 FR 32089, Nov. 20, 1973. Redesignated and amended at 41 FR 10770, Mar. 12, 1976; 49 FR 23834, June 8, 1984; 50 FR 4140, Jan. 29, 1985; 55 FR 11013, Mar. 26, 1990; 59 FR 49351, Sept. 28, 1994]

§ 640.76 Products stored or shipped at unacceptable temperatures.

(a) *Storage temperature.* (1) Except as provided in paragraph (a)(2) of this section, Source Plasma intended for manufacture into injectable products that is inadvertently exposed (i.e., an unforeseen occurrence in spite of compliance with good manufacturing practice) to a storage temperature warmer than −20 °C and colder than +10 °C may be issued only if labeled as ''Source Plasma Salvaged.'' The label shall be revised before issuance, and appropriate records shall be maintained identifying the units involved, describing their disposition, and explaining fully the conditions that caused the inadvertent temperature exposure.

(2) Source Plasma intended for manufacture into injectable products that is exposed inadvertently (i.e., an unforeseen occurrence in spite of compliance with good manufacturing practice) to one episode of storage temperature fluctuation that is warmer than −20 °C and colder than −5 °C for not more than 72 hours is exempt from the labeling requirements of paragraph (a)(1) of this section, provided that the plasma has been and remains frozen solid. Appropriate records shall be maintained identifying the units involved, describing their disposition, explaining fully the conditions that caused the inadvertent temperature exposure, and documenting that the episode of temperature elevation did not exceed 72 hours, that the temperature did not rise to warmer than −5 °C in storage, and that the plasma remained frozen solid throughout the period of elevated temperature. When requested, copies of the records shall be provided to the plasma derivative manufacturer.

(b) *Shipping temperature.* If Source Plasma for manufacture into injectable products is exposed inadvertently (i.e., an unforeseen occurrence in spite of compliance with good manufacturing practice) to a shipping temperature warmer than −5 °C and colder than +10 °C, the plasma derivative manufacturer shall label it ''Source Plasma Salvaged.'' Appropriate records shall be maintained identifying the units involved, describing their disposition, and explaining fully the conditions that caused the inadvertent temperature exposure.

(c) *Relabeling.* If Source Plasma is required to be relabeled as ''Source Plasma Salvaged'' under paragraph (a)(1) or (b) of this section, the person responsible for the relabeling shall cover the original label with either (1) a complete new label containing the appropriate information or (2) a partial label affixed to the original label and containing the appropriate new information, which covers the incorrect information regarding storage temperature.

[45 FR 80501, Dec. 5, 1980, as amended at 50 FR 4140, Jan. 29, 1985]

Subpart H—Albumin (Human)

§ 640.80 Albumin (Human).

(a) *Proper name and definition.* The proper name of the product shall be Albumin (Human). The product is defined as a sterile solution of the albumin component of human blood.

(b) *Source material.* The source material of Albumin (Human) shall be blood, plasma, serum or placentas from human donors determined at the time of donation to have been free from disease-causative agents that are not destroyed or removed by the processing

method, as determined by the medical history of the donor and from such physical examination and clinical tests as may appear necessary for each donor at the time the blood was obtained. Where source material is a product for which additional standards are effective, the requirements of those additional standards shall determine the propriety of the source material for use in the production of Albumin (Human). Where no additional standards are effective with respect to source material for the production of Albumin (Human), such source material shall:

(1) Be collected by a procedure which is designed to assure the integrity and to minimize the risk of contamination of the source material. The manufacturer of Albumin (Human) shall ensure that the collection procedure shall be as described in its license.

(2) Be identified to relate it accurately to the individual donor and the dates of collection.

(3) Not contain a preservative.

(4) Be stored and transported in a manner designed to prevent contamination by microorganisms, pyrogens, or other impurities.

(c) *Additives in source material.* Source material shall not contain an additive unless it is shown that the processing method yields a final product free of the additive to such extent that the continued safety, purity, potency, and effectiveness of the final product will not be adversely affected.

[42 FR 27582, May 31, 1977, as amended at 50 FR 4140, Jan. 29, 1985]

§ 640.81 Processing.

(a) *Date of manufacture.* The date of manufacture shall be the date of final sterile filtration of a uniform pool of bulk solution.

(b) *Processing method.* The processing method shall not affect the integrity of the product, and shall have been shown to yield consistently a product which is safe for intravenous injection.

(c) *Microbial contamination.* All processing steps shall be conducted in a manner to minimize the risk of contamination from either microorganisms or other deleterious matter. Preservatives to inhibit growth of microorganisms shall not be used during processing.

(d) *Storage of bulk fraction.* Bulk concentrate to be held more than 1 week prior to further processing shall be stored in clearly identified closed vessels at a temperature of −5 °C or colder. Any other bulk form of the product, exclusive of the sterile bulk solution, to be held more than 1 week prior to further processing shall be stored in clearly identified closed vessels at a temperature of 5 °C or colder. Any bulk fraction to be held one week or less prior to further processing shall be stored in clearly identified closed vessels at a temperature of 5 °C or colder.

(e) *Heat treatment.* Heating of the final containers of Albumin (Human) shall begin within 24 hours after completion of filling. Heat treatment shall be conducted so that the solution is heated for not less than 10 or more than 11 hours at an attained temperature of 60°±0.5 °C.

(f) *Stabilizer.* Either 0.16 millimole sodium acetyltryptophanate, or 0.08 millimole sodium acetyltryptophanate and 0.08 millimole sodium caprylate shall be added per gram of albumin as a stabilizer.

(g) *Incubation.* All final containers of Albumin (Human) shall be incubated at 20 to 35 °C for at least 14 days following the heat treatment prescribed in paragraph (e) of this section. At the end of this incubation period, each final container shall be examined and all containers showing any indication of turbidity or microbial contamination shall not be issued. The contents of turbid final containers shall be examined microscopically and tested for sterility. If growth occurs, organisms shall be identified as to genus, and the material from such containers shall not be used for further manufacturing.

[42 FR 27582, May 31, 1977, as amended at 50 FR 4140, Jan. 29, 1985]

§ 640.82 Tests on final product.

Tests shall be performed on the final product to determine that it meets the following standards:

(a) *Protein content.* Final product shall conform to one of the following concentrations: 4.0±0.25 percent; 5.0±0.30 percent; 20.0±1.2 percent; and 25.0±1.5 percent solution of protein.

(b) *Protein composition.* At least 96 percent of the total protein in the final

product shall be albumin, as determined by a method that has been approved for each manufacturer by the Director, Center for Biologics Evaluation and Research, Food and Drug Administration.

(c) *Hydrogen ion concentration.* The pH shall be 6.9±0.5 when measured in a solution of the final product diluted to a concentration of 1 percent protein with 0.15 molar sodium chloride.

(d) *Sodium content.* The sodium content of the final product shall be 130 to 160 milliequivalents per liter.

(e) *Heme content.* The absorbance at 403 nanometers of a solution of the final product diluted to a concentration of 1 percent protein in a cell with a 1-centimeter light path shall not exceed 0.25.

(f) *Heat stability.* A final container sample of Albumin (Human) shall remain unchanged, as determined by visual inspection, after heating at 57 °C for 50 hours, when compared to its control consisting of a sample, from the same lot, which has not undergone this heating.

[42 FR 27582, May 31, 1977, as amended at 49 FR 23834, June 8, 1984; 50 FR 4140, Jan. 29, 1985; 55 FR 11013, Mar. 26, 1990]

§ 640.83 General requirements.

(a) *Preservative.* The final product shall not contain a preservative.

(b) *Storage of bulk solution.* After all processing steps have been completed, the sterile bulk solution shall be stored in a manner that will ensure the continued sterility of the product, and at a temperature that shall not exceed the recommended storage temperature of the final product prescribed in §610.53 of this chapter.

[42 FR 27582, May 31, 1977]

§ 640.84 Labeling.

In addition to the labeling requirements of §§610.60, 610.61, and 610.62 of this chapter,

(a) The container and package labels shall contain the following information:

(1) The osmotic equivalent in terms of plasma, and the sodium content in terms of a value or a range in milliequivalents per liter;

(2) The cautionary statement placed in a prominent position on the label, ''Do Not Use if Turbid. Do Not Begin Administration More Than 4 Hours After the Container Has Been Entered.'';

(3) The need for additional fluids when 20 percent or 25 percent albumin is administered to a patient with marked dehydration;

(4) The protein content, expressed as a 4 percent, 5 percent, 20 percent, or 25 percent solution.

(b) The type of source material, expressed as venous plasma, placental plasma, or both, used to manufacture the final product shall appear on either the container or package label or in the package insert.

[42 FR 27582, May 31, 1977, as amended at 49 FR 2244, Jan. 19, 1984]

Subpart I—Plasma Protein Fraction (Human)

SOURCE: 42 FR 27583, May 31, 1977, unless otherwise noted.

§ 640.90 Plasma Protein Fraction (Human).

(a) *Proper name and definition.* The proper name of the product shall be Plasma Protein Fraction (Human). The product is defined as a sterile solution of protein composed of albumin and globulin, derived from human blood.

(b) *Source material.* The source material of Plasma Protein Fraction (Human) shall be blood, plasma, or serum from human donors determined at the time of donation to have been free from disease-causative agents that are not destroyed or removed by the processing method, as determined by the medical history of the donor and from such physical examination and clinical tests as may appear necessary for each donor at the time the blood was obtained. When source material is a product for which additional standards are effective, the requirements of those additional standards shall determine the propriety of the material for use in the production of Plasma Protein Fraction (Human). When no additional standards are effective with respect to source material for the production of Plasma Protein Fraction (Human), such source material shall:

(1) Be collected by a procedure which is designed to assure the integrity and to minimize the risk of contamination of the source material. The manufacturer of Plasma Protein Fraction (Human) shall ensure that the collection procedure shall be as described in its license;

(2) Be identified to relate it accurately to the individual donor and to the dates of collection;

(3) Not contain a preservative; and

(4) Be stored and transported in a manner designed to prevent contamination by microorganisms, pyrogens, or other impurities.

(c) *Additives in source material.* Source material shall not contain an additive unless it is shown that the processing method yields a final product free of the additive to such extent that the continued safety, purity, potency, and effectiveness of the final product will not be adversely affected.

§ 640.91 Processing.

(a) *Date of manufacture.* The date of manufacture shall be the date of final sterile filtration of a uniform pool of bulk solution.

(b) *Processing method.* The processing method shall not affect the integrity of the product, and shall have been shown to yield consistently a product which:

(1) After the heating prescribed in paragraph (e) of this section does not show an increase in the components with electrophoretic mobility similar to that of alpha globulin that amounts to more than 5 percent of the total protein.

(2) Contains less than 5 percent protein with a sedimentation coefficent greater than 7.0 S.

(3) Is safe for intravenous injection.

(c) *Microbial contamination.* All processing steps shall be conducted in a manner to minimize the risk of contimination from either microorganisms or other deleterious matter. Preservatives to inhibit growth of microorganisms shall not be used during processing.

(d) *Storage of bulk fraction.* Bulk concentrate to be held more than 1 week prior to further processing shall be stored in clearly identified closed vessels at a temperature of −5 °C or colder. Any other bulk form of the product (exclusive of the sterile bulk solution) to be held more than 1 week prior to further processing, shall be stored in clearly identified closed vessels at a temperature of 5 °C or colder. Any bulk fraction to be held one week or less prior to further processing shall be stored in clearly identified closed vessels at a temperature of 5 °C or colder.

(e) *Heat treatment.* Heating of the final containers of Plasma Protein Fraction (Human) shall begin within 24 hours after completion of filling. Heat treatment shall be conducted so that the solution is heated for not less than 10 or more than 11 hours at an attained temperature of 60°±0.5 °C.

(f) *Stabilizer.* Either 0.16 millimole sodium acetyltryptophanate, or 0.08 millimole sodium acetyltryptophanate and 0.08 millimole sodium caprylate shall be added per gram of protein as a stabilizer.

(g) *Incubation.* All final containers of Plasma Protein Fraction (Human) shall be incubated at 20 to 35 °C for at least 14 days following the heat treatment prescribed in paragraph (e) of this section. At the end of this incubation period, each final container shall be examined and all containers showing any indication of turbidity or microbial contamination shall not be issued. The contents of turbid final containers shall be examined microscopically and tested for sterility. If growth occurs, the types of organisms shall be identified as to genus and the material from such containers shall not be used for further manufacturing.

§ 640.92 Tests on final product.

Tests shall be performed on the final product to determine that it meets the following standards:

(a) *Protein content.* The final product shall be a 5.0±0.3 percent solution of protein.

(b) *Protein composition.* The total protein in the final product shall consist of at least 83 percent albumin, and no more than 17 percent globulins. No more than 1 percent of the total protein shall be gamma globulin. The protein composition shall be determined by a method that has been approved for each manufacturer by the Director, Center for Biologics Evaluation and

Research, Food and Drug Administration.

(c) *Hydrogen ion concentration.* The pH shall be 7.0±0.3 when measured in a solution of the final product diluted to a concentration of 1 percent protein with 0.15 molar sodium chloride.

(d) *Sodium content.* The sodium content of the final product shall be 130 to 160 milliequivalents per liter.

(e) *Potassium content.* The potassium content of the final product shall not exceed 2 milliequivalents per liter.

(f) *Heat stability.* A final container sample of Plasma Protein Fraction (Human) shall remain unchanged, as determined by visual inspection, after heating at 57 °C for 50 hours, when compared to its control consisting of a sample, from the same lot, which has not undergone this heating.

[42 FR 27583, May 31, 1977, as amended at 49 FR 23834, June 8, 1984; 55 FR 11013, Mar. 26, 1990]

§ 640.93 General requirements.

(a) *Preservative.* The final product shall not contain a preservative.

(b) *Storage of bulk solution.* After all processing steps have been completed, the sterile bulk solution shall be stored in a manner that will ensure the continued sterility of the product, and at a temperature that shall not exceed the recommended storage temperature of the final product prescribed in §610.53 of this chapter.

§ 640.94 Labeling.

In addition to the labeling requirements of §§610.60, 610.61, and 610.62 of this chapter, the container and package labels shall contain the following information:

(a) The osmotic equivalent in terms of plasma, and the sodium content in terms of a value or a range in milliequivalents per liter.

(b) The cautionary statement placed in a prominent position on the label, ''Do Not Use if Turbid. Do Not Begin Administration More than 4 Hours After the Container Has Been Entered.''

[42 FR 27583, May 31, 1977, as amended at 49 FR 2244, Jan. 19, 1984]

Subpart J—Immune Globulin (Human)

§ 640.100 Immune Globulin (Human).

(a) *Proper name and definition.* The proper name of this product shall be Immune Globulin (Human). The product is defined as a sterile solution containing antibodies derived from human blood.

(b) *Source material.* The source of Immune Globulin (Human) shall be blood, plasma or serum from human donors determined at the time of donation to have been free of causative agents of diseases that are not destroyed or removed by the processing methods, as determined by the donor's history and from such physical examination and clinical tests as appear necessary for each donor at the time the blood was obtained. The source blood, plasma or serum shall not contain a preservative and shall be stored in a manner that will prevent contamination by microorganisms, pyrogens or other impurities.

(c) *Additives in source material.* Source blood, plasma or serum shall contain no additives other than citrate or acid citrate dextrose anticoagulant solution, unless it is shown that the processing method yields a product free of the additive to such an extent that the safety, purity and potency of the product will not be affected adversely.

[38 FR 32089, Nov. 20, 1973, as amended at 50 FR 4140, Jan. 29, 1985]

§ 640.101 General requirements.

(a) *Heat stability test.* Approximately 2 ml. of completely processed material of each lot shall not show any visible sign of gelation after heating in a 12 x 75 mm. stoppered glass tube at 57 °C. for 4 hours.

(b) *Hydrogen ion concentration.* The pH of final container material shall be 6.8±0.4 when measured in a solution diluted to 1 percent protein with 0.15 molar sodium chloride.

(c) *Turbidity.* The product shall be free of turbidity as determined by visual inspection of final containers.

(d) *Date of manufacture.* The date of manufacture is the date of initiating the last valid measles or poliomyelitis

antibody test (§ 640.104(b) (2) and (3)) whichever date is earlier.

(e) *Labeling.* In addition to complying with all applicable labeling required in this subchapter, labeling shall indicate that:

(1) There is no prescribed potency for viral hepatitis antibodies.

(2) The product is not recommended for intravenous administration.

(3) The lot is or is not suitable for use with Measles Virus Vaccine Live.

(4) The lot is or is not recommended for poliomyelitis.

(f) *Samples and protocols.* For each lot of Immune Globulin (Human) the following material shall be submitted to the Director, Center for Biologics Evaluation and Research, Food and Drug Administration, 8800 Rockville Pike, Bethesda, MD 20892:

(1) A 50 ml. sample of the final product.

(2) All protocols relating to the history of each lot and all results of all tests prescribed in these additional standards.

[38 FR 32089, Nov. 20, 1973; 48 FR 13026, Mar. 29, 1983, as amended at 49 FR 23834, June 8, 1984; 50 FR 4140, Jan. 29, 1985; 51 FR 15611, Apr. 25, 1986; 55 FR 11013, Mar. 26, 1990]

§ 640.102 Manufacture of Immune Globulin (Human).

(a) *Processing method.* The processing method shall be one that has been shown: (1) To be capable of concentrating tenfold from source material at least two different antibodies; (2) not to affect the integrity of the globulins; (3) to consistently yield a product which is safe for subcutaneous and intramuscular injection and (4) not to transmit viral hepatitis.

(b) *Microbial contamination.* Low temperatures or aseptic techniques shall be used to minimize contamination by microorganisms. Preservatives to inhibit growth of microorganisms shall not be used during processing.

(c) *Bulk storage.* The globulin fraction may be stored in bulk prior to further processing provided it is stored in clearly identified hermetically closed vessels. Globulin as either a liquid concentrate or a solid and containing alcohol or more than 5 percent moisture shall be stored at a temperature of −10 °C. or lower. Globulin as a solid free from alcohol and containing less than 5 percent moisture, shall be stored at a temperature of 0 °C. or lower.

(d) *Determination of the lot.* Each lot of Immune Globulin (Human) shall represent a pooling of approximately equal amounts of material from not less than 1,000 donors.

(e) *Sterilization and heating.* The final product shall be sterilized promptly after solution. At no time during processing shall the product be exposed to temperatures above 45 °C. and after sterilization the product shall not be exposed to temperatures above 30 to 32 °C. for more than 72 hours.

[38 FR 32089, Nov. 20, 1973, as amended at 50 FR 4140, Jan. 29, 1985]

§ 640.103 The final product.

(a) *Final solution.* The final product shall be a 16.5±1.5 percent solution of globulin containing 0.3 molar glycine and a preservative.

(b) *Protein composition.* At least 90 percent of the globulin shall have an electrophoretic mobility not faster than -2.8×10^{-5} centimeters^2 per volt per second, when measured at a 1 percent protein concentration in sodium diethylbarbiturate buffer at pH 8.6 and 0.1 ionic strength.

§ 640.104 Potency.

(a) *Antibody levels and tests.* Each lot of final product shall contain at least the minimum levels of antibodies for diphtheria, measles, and for at least one type of poliomyelitis. In the event the final bulk solution is stored at a temperature above 5 °C. the antibody level tests shall be performed after such storage with a sample of the stored material.

(b) *Minimum levels.* The minimum antibody levels are as follows:

(1) No less than 2 units of diphtheria antitoxin per ml.

(2) A measles neutralizing antibody level of no less than 0.50 times the level of the Reference Immune Serum Globulin, except that when recommended for use with Measles Virus Vaccine Live, the measles antibody level shall be as prescribed in § 640.114.

(3) A poliomyelitis neutralizing antibody level of no less than 1.0 for Type 1, 1.0 for Type 2, and 2.5 for Type 3,

times the antibody level of the Reference Immune Serum Globulin.

(c) *Reference materials.* The following reference materials shall be obtained from the Center for Biologics Evaluation and Research:

(1) Reference Immune Serum Globulin for correlation of measles antibody titers.

(2) Reference Immune Serum Globulin for correlation of poliomyelitis antibody titers, Types 1, 2, and 3.

[38 FR 32089, Nov. 20, 1973, as amended at 39 FR 9661, Mar. 13, 1974; 49 FR 23834, June 8, 1984; 50 FR 4140, Jan. 29, 1985; 55 FR 11013, Mar. 26, 1990]

Subpart K [Reserved]

Subpart L—Alternative Procedures

§ 640.120 Alternative procedures.

(a) The Director, Center for Biologics Evaluation and Research, may approve an exception or alternative to any requirement in subchapter F of chapter I of title 21 of the Code of Federal Regulations regarding blood, blood components, or blood products. Requests for such exceptions or alternatives shall ordinarily be in writing. Licensed establishments shall submit such requests in accordance with §601.12 of this chapter. However, in limited circumstances, such requests may be made orally and permission may be given orally by the Director. Oral requests and approvals must be promptly followed by written requests and written approvals.

(b) FDA will publish a list of approved alternative procedures and exceptions periodically in the FEDERAL REGISTER.

[55 FR 10423, Mar. 21, 1990, as amended at 62 FR 39903, July 24, 1997]

PART 660—ADDITIONAL STANDARDS FOR DIAGNOSTIC SUBSTANCES FOR LABORATORY TESTS

Subpart A—Antibody to Hepatitis B Surface Antigen

Sec.

Subpart B [Reserved]

Subpart C—Blood Grouping Reagent

Subpart D—Reagent Red Blood Cells

Subpart E—Hepatitis B Surface Antigen

Subpart F—Anti-Human Globulin

AUTHORITY: 21 U.S.C. 321, 351, 352, 353, 355, 360, 371; 42 U.S.C. 216, 262, 263, 263a, 264.

CROSS REFERENCES: For U.S. Customs Service regulations relating to viruses, serums, and toxins, see 19 CFR 12.21–12.23. For U.S. Postal Service regulations relating to the admissibility to the United States mails see parts 124 and 125 of the Domestic Mail Manual, that is incorporated by reference in 39 CFR part 111.

Subpart A—Antibody to Hepatitis B Surface Antigen

§ 660.1 Antibody to Hepatitis B Surface Antigen.

(a) *Proper name and definition.* The proper name of this product shall be

Antibody to Hepatitis B Surface Antigen. The product is defined as a preparation of serum containing antibody to hepatitis B surface antigen.

(b) *Source.* The source of this product shall be plasma or blood, obtained aseptically from animals immunized with hepatitis B surface antigen, which have met the applicable requirements of § 600.11 of this chapter, or from human donor whose blood is positive for hepatitis B surface antigen.

[40 FR 29711, July 15, 1975]

§ 660.2 General requirements.

(a) *Processing.* The processing method shall be one that has been shown to consistently yield a specific and potent final product free of properties which would adversely affect the test results when the product is tested by the methods recommended by the manufacturer in the package enclosure.

(b) *Ancillary reagents and materials.* All ancillary reagents and materials supplied in the package with the product shall meet generally accepted standards of purity and quality and shall be effectively segregated and otherwise manufactured in a manner (such as heating at 60 °C. for 10 hours) that will reduce the risk of contaminating the product and other biological products. Ancillary reagents and materials accompanying the product which are used in the performance of the test as described by the manufacturer's recommended test procedures shall have been shown not to adversely affect the product within the prescribed dating period.

(c) *Labeling.* In addition to the items required by other applicable labeling provisions of this subchapter, the following shall also be included:

(1) Indication of the source of the product immediately following the proper name on both the final container and package label, e.g., human, guinea pig.

(2) Name of the test method(s) recommended for the product on the package label and on the final container label when capable of bearing a full label (see § 610.60(a) of this chapter).

(3) A warning on the package label and on the final container label if capable of bearing a full label (see § 610.60(a) of this chapter) indicating that the product and antigen if supplied, shall be handled as if capable of transmitting hepatitis.

(4) If the product is dried, the final container label shall indicate ''Reconstitution date: _____'' and a statement indicating the period within which the product may be used after reconstitution.

(5) The package shall include a package enclosure providing (i) adequate instructions for use, (ii) a description of all recommended test methods, and (iii) warnings as to possible hazards, including hepatitis, in handling the product and any ancillary reagents and materials accompanying the product.

(d) *Final container.* A final container shall be sufficiently transparent to permit visual inspection of the contents for presence of particulate matter and increased turbidity. The effectiveness of the contents of a final container shall be maintained throughout its dating period.

(e) *Date of manufacture.* The date of manufacture of Antibody to Hepatitis B surface Antigen that has been iodinated with radioactive iodine (^{125}I) shall be the day of labeling the antibody with the radionuclide.

(f) *Retention samples.* Each manufacturer shall retain representative samples of the product in accordance with § 600.13 of this chapter except for that which has been iodinated with radioactive iodine. Retention samples of Antibody to Hepatitis B Surface Antigen iodinated with ^{125}I shall consist of a minimum of two complete finished packages of each lot of the diagnostic test kit and shall be retained for a period of at least 90 days from the date of manufacture.

[38 FR 32098, Nov. 20, 1973, as amended at 40 FR 29711, July 15, 1975; 46 FR 36134, July 14, 1981; 49 FR 1684, Jan. 13, 1984]

§ 660.3 Reference panel.

A Reference Hepatitis B Surface Antigen Panel shall be obtained from the Center for Biologics Evaluation and Research and shall be used for determining the potency and specificity of Antibody to Hepatitis B Surface Antigen.

[40 FR 29711, July 15, 1975, as amended at 49 FR 23834, June 8, 1984; 55 FR 11013, Mar. 26, 1990]

§ 660.4 Potency test.

To be satisfactory for release, each filling of Antibody to Hepatitis B Surface Antigen shall be tested against the Reference Hepatitis B Surface Antigen Panel and shall be sufficiently potent to detect the antigen in the appropriate sera of the reference panel by all test methods recommended by the manufacturer in the package insert.

[40 FR 29711, July 15, 1975]

§ 660.5 Specificity.

Each filling of the product shall be specific for antibody to hepatitis B surface antigen, as determined by specificity tests found acceptable by the Director, Center for Biologics Evaluation and Research.

[40 FR 29712, July 15, 1975, as amended at 49 FR 23834, June 8, 1984; 55 FR 11013, Mar. 26, 1990]

§ 660.6 Samples; protocols; official release.

(a) *Samples.* (1) For the purposes of this section, a sample of product not iodinated with ^{125}I means a sample from each filling of each lot packaged as for distribution, including all ancillary reagents and materials; and a sample of product iodinated with ^{125}I means a sample from each lot of diagnostic test kits in a finished package, including all ancillary reagents and materials.

(2) Unless the Director, Center for Biologics Evaluation and Research, determines that the reliability and consistency of the finished product can be assured with a smaller quantity of sample or no sample and specifically reduces or eliminates the required quantity of sample, each manufacturer shall submit the following samples to the Director, Center for Biologics Evaluation and Research (HFB–1), 8800 Rockville Pike, Bethesda, MD 20892, within 5 working days after the manufacturer has satisfactorily completed all tests on the samples:

(i) One sample until written notification of official release is no longer required under paragraph (c)(2) of this section.

(ii) One sample at periodic intervals of 90 days, beginning after written notification of official release is no longer required under paragraph (c)(2) of this section. The sample submitted at the 90-day interval shall be from the first lot or filling, as applicable, released by manufacturer, under the requirements of §610.1 of this chapter, after the end of the previous 90-day interval. The sample shall be identified as ''surveillance sample'' and shall include the date of manufacture.

(iii) Samples may at any time be required to be submitted to the Director, Center for Biologics Evaluation and Research, if the Director finds that continued evaluation is necessary to ensure the potency, quality, and reliability of the product.

(b) *Protocols.* For each sample submitted as required in paragraph (a)(1) of this section, the manufacturer shall send a protocol that consists of a summary of the history of manufacture of the product, including all results of each test for which test results are requested by the Director, Center for Biologics Evaluation and Research. The protocols submitted with the samples at periodic intervals as provided in paragraph (a)(2)(ii) of this section shall be identified by the manufacturer as ''surveillance test results.''

(c) *Offical release.* (1) The manufacturer shall not distribute the product until written notification of official release is received from the Director, Center for Biologics Evaluation and Research, except as provided in paragraph (c)(2) of this section. Official release is required for samples from at least five consecutive lots or fillings, as applicable, manufactured after licensure of the product.

(2) After written notification of official release is received from the Director, Center for Biologics Evaluation and Research, for at least five consecutive lots or fillings, as applicable, manufactured after licensure of the product, and after the manufacturer receives from the Director, Center for Biologics Evaluation and Research, written notification that official release is no longer required, subsequent lots or fillings may be released by the manufacturer under the requirements of §610.1 of this chapter.

(3) The manufacturer shall not distribute lots or fillings, as applicable, of

products that required sample submission under paragraph (a)(2)(iii) of this section until written notification of official release or notification that official release is no longer required is received from the Director, Center for Biologics Evaluation and Research.

[48 FR 20407, May 6, 1983, as amended at 49 FR 23834, June 8, 1984; 51 FR 15611, Apr. 25, 1986; 55 FR 11013 and 11014, Mar. 26, 1990]

Subpart B [Reserved]

Subpart C—Blood Grouping Reagent

SOURCE: 53 FR 12764, Apr. 19, 1988, unless otherwise noted.

§ 660.20 Blood Grouping Reagent.

(a) *Proper name and definition.* The proper name of this product shall be Blood Grouping Reagent and it shall consist of an antibody-containing fluid prepared by a method demonstrated to yield consistently a sterile product and containing one or more of the blood grouping antibodies listed in § 660.28(d).

(b) *Source.* The source of this product shall be blood, plasma, serum, or protein-rich fluids, such as those derived from stable immunoglobulin-secreting cell lines maintained either in tissue cultures or in secondary hosts.

§ 660.21 Processing.

(a) *Processing method.* (1) The processing method shall be one that has been shown to yield consistently a specific, potent final product, free of properties that would affect adversely the intended use of the product throughout its dating period. Stability testing shall be performed on an adequate number of representative samples of each group of products manufactured in the same fashion.

(2) Only that material that has been fully processed, thoroughly mixed in a single vessel, and sterile filtered shall constitute a lot.

(3) A lot may be subdivided into clean, sterile vessels. Each subdivision shall constitute a sublot. If lots are to be subdivided, the manufacturer shall include this information in the license application. The manufacturer shall describe the test specifications to verify that each sublot is identical to other sublots of the lot.

(4) Each lot of Blood Grouping Reagent shall be identified by a lot number. Each sublot shall be identified by that lot number to which a distinctive prefix or suffix shall be added. Final container and package labels shall bear the lot number and all distinctive prefixes and suffixes that have been applied to identify the sublot from which filling was accomplished.

(b) *Color coding of reagents.* Blood Grouping Reagents may be colored provided the added colorant does not adversely affect the safety, purity, or potency of the product and the colorant is approved by the Director, Center for Biologics Evaluation and Research (HFN–830), Food and Drug Administration, 8800 Rockville Pike, Bethesda, MD 20892.

(c) *Final containers and dropper assemblies.* Final containers and dropper pipettes shall be colorless and sufficiently transparent to permit observation of the contents to detect particulate matter or increased turbidity during use.

(d) *Volume of final product.* Each manufacturer shall identify the possible final container volumes in the product license application.

(e) *Date of manufacture.* The date of manufacture shall be the date the manufacturer begins the last entire group of potency tests.

(Information collection requirements approved by the Office of Management and Budget under control number 0910–0209)

§ 660.22 Potency requirements with reference preparations.

(a) *Potency requirements.* Products for which reference Blood Grouping Reagents are available shall have a potency titer value at least equal to that of the reference preparation.

(b) *Reference preparations.* Reference Blood Grouping Reagents shall be obtained from the Center for Biologics Evaluation and Research (HFN–890), Food and Drug Administration, 8800 Rockville Pike, Bethesda, MD 20892, and shall be used as described in the accompanying package insert for determining the potency of Blood Grouping Reagents.

(Information collection requirements approved by the Office of Management and Budget under control number 0910–0209)

§ 660.25 Potency tests without reference preparations.

Products for which Reference Blood Grouping Reagents are not available shall be tested for potency by a method approved by the Director, Center for Biologics Evaluation and Research (HFN–830), Food and Drug Administration, 8800 Rockville Pike, Bethesda, MD 20892.

(a) *Potency requirements.* Blood Grouping Reagents recommended for the test tube methods, including the indirect antiglobulin tests, shall have the following potency titer values, unless other values are approved by the Director, Center for Biologics Evaluation and Research (HFN–830), Food and Drug Administration, 8800 Rockville Pike, Bethesda, MD 20892.

(1) For Anti-K, Anti-$\bar{k}$, Anti-Jk^a, Anti-Fy^a, Anti-C^w, at least 1+ reaction with a 1:8 dilution of the reagent.

(2) For Anti-S, Anti-$\bar{s}$, Anti-P_1, Anti-M, Anti-I, Anti-e (saline), Anti-$\bar{c}$ (saline), and Anti-A_1, at least 1+ reaction with a 1:4 dilution of the reagent.

(3) For Anti-U, Anti-Kp^a, Anti-Kp^b, Anti-Js^a, Anti-Js^b, Anti-Fy^b, Anti-N, Anti-Le^a, Anti-Le^b, Anti-Lu^a, Anti-Lu^b, Anti-Di^a, Anti-M^g, Anti-Jk^b, Anti-Co^b, Anti-Wr^a, and Anti-Xg^a, at least 2+ reaction with undiluted reagent.

(b) *Products recommended for slide tests or microplate techniques.* Blood Grouping Reagent recommended for slide test methods or microplate techniques shall produce clearly positive macroscopic results when both undiluted reagent and reagent diluted with an equal volume of diluent are tested by all methods recommended in the manufacturer's package insert using red blood cells showing heterozygous or diminished expression of the corresponding antigen. The dilution shall be made with an equal volume of compatible serum or approved diluent.

(c) *Products recomended for use in an automated system.* The manufacturer of Blood Grouping Reagent that is recommended for use in an automated system shall demonstrate that its product when used both undiluted and diluted with an equal volume of diluent satisfactorily performs when tested with cells representing heterozygous or diminished expression of the corresponding antigen.

(Information collection requirements approved by the Office of Management and Budget under control number 0910–0209)

§ 660.26 Specificity tests and avidity tests.

Specificity and avidity tests shall be performed using test procedures approved by the Director, Center for Biologics Evaluation and Research (HFN–830), Food and Drug Administration, 8800 Rockville Pike, Bethesda, MD 20892.

(Information collection requirements approved by the Office of Management and Budget under control number 0910–0209)

§ 660.28 Labeling.

In addition to the applicable labeling requirements of §§ 610.62 through 610.65 and § 809.10, and in lieu of the requirements in §§ 610.60 and 610.61, the following requirements shall be met:

(a) *Final container label*—(1) *Color coding.* The final container label of all Blood Grouping Reagents shall be completely white, except that all or a portion of the final container label of the following Blood Grouping Reagents may be color coded with the specified color which shall be a visual match to a specific color sample designated by the Director, Center for Biologics Evaluation and Research (HFN–830), Food and Drug Administration, 8800 Rockville Pike, Bethesda, MD 20892. Printing on all final container labels shall be in solid black. A logo or company name may be placed on the final container label; however, the logo or company name shall be located along the bottom or end of the label, outside the main panel.

Blood grouping reagent	Color of label paper
Anti-A	Blue.
Anti-B	Yellow.
Slide and rapid tube test blood grouping reagents only:	
Anti-C	Pink.
Anti-D	Gray.
Anti-E	Brown.
Anti-CDE	Orange.
Anti-$\bar{c}$	Lavender.

Blood grouping reagent	Color of label paper
Anti-e	Green.

(2) *Required information.* The proper name ''Blood Grouping Reagent'' need not appear on the final container label provided the final container is distributed in a package and the package label bears the proper name. The final container label shall bear the following information:

(i) Name of the antibody or antibodies present as set forth in paragraph (d) of this section.

(ii) Name, address (including ZIP code), and license number of the manufacturer.

(iii) Lot number, including sublot designations.

(iv) Expiration date.

(v) Source of product if other than human plasma or serum.

(vi) Test method(s) recommended.

(vii) Recommended storage temperature in degrees Celsius.

(viii) Volume of product if a liquid, or equivalent volume for a dried product if it is to be reconstituted.

(ix) If a dried product, to remind users to record the reconstitution date on the label, the statement ''RECONSTITUTION DATE _____. EXPIRES 1 YEAR AFTER RECONSTITUTION DATE.''

(3) *Lettering size.* The type size for the specificity of the antibody designation on the labels of a final container with a capacity of less than 5 milliliters shall be not less than 12 point. The type size for the specificity of the antibody designations on the label of a container with a capacity of 5 milliliters or more shall be not less than 18 point.

(4) *Visual inspection.* When the label has been affixed to the final container, a sufficient area of the container shall remain uncovered for its full length or no less than 5 millimeters of the lower circumference to permit inspection of the contents. The label on a final product container for antibodies Anti-c, Anti-k, or Anti-s shall display a bar immediately over the specificity letter used in the name, i.e., Anti-$\bar{c}$, Anti-k, or Anti-$\bar{s}$.

(b) *Package label.* The following information shall appear either on the package label or on the final container label if it is visible within the package.

(1) Proper name of the product.

(2) Name of the antibody or antibodies present as set forth in paragraph (d) of this section.

(3) Name, address (including ZIP Code), and license number of the manufacturer.

(4) Lot number, including sublot designations.

(5) Expiration date.

(6) Preservative used and its concentration.

(7) Number of containers, if more than one.

(8) Volume or equivalent volume for dried products when reconstituted, and precautions for adequate mixing when reconstituting.

(9) Recommended storage temperature in degrees Celsius.

(10) Source of the product if other than human serum or plasma.

(11) Reference to enclosed package insert.

(12) If a dried product, a statement indicating the period within which the product may be used after reconstitution.

(13) The statement: ''FOR IN VITRO DIAGNOSTIC USE.''

(14) The statement: ''MEETS FDA POTENCY REQUIREMENTS.''

(15) If human blood was used in manufacturing the product, the statement: ''CAUTION: ALL BLOOD PRODUCTS SHOULD BE TREATED AS POTENTIALLY INFECTIOUS. SOURCE MATERIAL FROM WHICH THIS PRODUCT WAS DERIVED WAS FOUND NEGATIVE WHEN TESTED IN ACCORDANCE WITH CURRENT FDA REQUIRED TESTS. NO KNOWN TEST METHODS CAN OFFER ASSURANCE THAT PRODUCTS DERIVED FROM HUMAN BLOOD WILL NOT TRANSMIT INFECTIOUS AGENTS.''

(16) A statement of an observable indication of an alteration of the product, e.g., turbidity, color change, precipitate, that may indicate possible deterioration of the product.

(c) *Package insert.* Each final container of Blood Grouping Reagent shall be accompanied by a package insert meeting the requirements of §809.10. If two or more final containers requiring identical package inserts are placed in

a single package, only one package insert per package is required.

(d) *Names of antibodies.*

BLOOD GROUP DESIGNATION FOR CONTAINER LABEL

Anti-A	Anti-Jk^b
Anti-A_1	Anti-Js^a
Anti-A, B	Anti-Js^b
Anti-A and B	Anti-K
Anti-B	Anti-k
Anti-C	Anti-Kp^a
Anti-C^w	Anti-Kp^b
Anti-$\bar{c}$	Anti-Le^a
Anti-CD	Anti-Le^b
Anti-CDE	Anti-Lu^a
Anti-Co^b	Anti-Lu^b
Anti-D	Anti-M
Anti-DE	Anti-M^g
Anti-Di^a	Anti-N
Anti-E	Anti-P_1
Anti-e	Anti-S
Anti-Fy^a	Anti-$\bar{s}$
Anti-Fy^b	Anti-U
Anti-I	Anti-Wr^a
Anti-Jk^a	Anti-Xg^a

[53 FR 12764, Apr. 19, 1988, as amended at 59 FR 23637, May 6, 1994]

(Information collection requirements approved by the Office of Management and Budget under control number 0910–0209)

Subpart D—Reagent Red Blood Cells

SOURCE: 52 FR 37450, Oct. 7, 1987, unless otherwise noted.

§ 660.30 Reagent Red Blood Cells.

(a) *Proper name and definition.* The proper name of the product shall be Reagent Red Blood Cells, which shall consist of a preparation of human red blood cells used to detect or identify human blood-group antibodies.

(b) *Source.* Reagent Red Blood Cells shall be prepared from human peripheral blood meeting the criteria of §§ 660.31 and 660.32, or from umbilical cord cells which shall be collected and prepared according to the manufacturer's product license application.

§ 660.31 Suitability of the donor.

Donors of peripheral blood for Reagent Red Blood Cells shall meet the criteria for donor suitability under § 640.3 of this chapter, except that paragraphs (b)(5) and (6), (d), and (e) of § 640.3 shall not apply.

§ 660.32 Collection of source material.

Blood for Reagent Red Blood Cells from donors of peripheral blood shall be collected as prescribed under § 640.4 of this chapter, except that paragraphs (c), (d), (g), and (h) of § 640.4 shall not apply.

§ 660.33 Testing of source material.

Except as provided in this section, a sample of each blood incorporated into the Reagent Red Blood Cell product shall be individually tested, with no fewer than two donor sources of each antibody specificity employed, to confirm the identification of all blood group antigens specified in the labeling as present or absent. The manufacturer shall perform at least one of the required tests for each factor. The Reagent Red Blood Cell product may be tested with a single donor source of antibody specificity if only one source of antibody is available, and the Director, Center for Biologics Evaluation and Research, has approved the use of a single donor source of antiserum. Each of these tests shall be conducted and interpreted independently, and any discrepancy between the results of these two tests shall be resolved by testing with at least one additional antiserum before concluding that the antigen is present or absent. Where fewer than three donor sources of an antibody specificity are available, test discrepancies shall be resolved in accordance with the manufacturer's product license application. Group O Reagent Red Blood Cells used in the detection or identification of unexpected antibodies shall include at least the following common antigens in each lot of the product: D, C, E, $\bar{c}$, e, K, k, Fy^a, Fy^b, Jk^a, Jk^b, Le^a, Le^b, P_1, M, N, S, and $\bar{s}$.

[52 FR 37450, Oct. 7, 1987, as amended at 55 FR 11013, Mar. 26, 1990]

§ 660.34 Processing.

(a) *Processing method.* The processing method shall be one that has been shown to yield consistently a product that is capable of detecting, throughout the dating period, alloantibodies corresponding to all required blood group antigens specified in the labeling as present.

(b) *Products prepared from pooled red blood cells.* If the product is recommended for the detection of unexpected antibodies, the pool shall be prepared by combining equal amounts of cells from no more than two donors. Umbilical cord cells are exempt from this requirement. Pooled cells shall not be recommended for pretransfusion tests, done in lieu of a major crossmatch, to detect unexpected antibodies in patients' samples.

(c) *Absence of antibodies.* Each lot of final product shall be free of demonstrable antibodies, including anti-A and anti-B, unless the package insert and container lable include instructions to wash the cells before use. The final product shall also be direct antiglobulin test negative when tested with polyspecific anti-human globulin.

(d) *Final container.* The final containers used for each lot of product shall be clean and shall permit observation of the contents for hemolysis or a change in color. The final container label, container cap, and dropper bulb of a Reagent Red Blood Cell product may be color-coded with a visual match to a specific color approved by the Director, Center for Biologics Evaluation and Research.

(e) *Date of manufacture.* The date of manufacture of the product shall be the date that the blood is withdrawn from the donor or obtained from umbilical cords. The period during which the reagent red blood cell source material is kept by the manufacturer in storage in a frozen state at −65 °C or colder is excluded from the dating period. If the product consists of red blood cells from two or more donors, the date of manufacture of the final product shall be the date of withdrawal of blood from the donor of the oldest constituent blood. When a product consists of more than one container, e.g., cell panel, the date of manufacture of each container of the product shall be the earliest date that blood was withdrawn from a donor for any container of the product.

(f) *Retention samples.* Retention samples shall be maintained as required by § 600.13 of this chapter, except that samples must be retained only throughout the dating period of the product.

(Approved by the Office of Management and Budget under control number 0910–0073)

[52 FR 37450, Oct. 7, 1987, as amended at 55 FR 11013, Mar. 26, 1990]

§ 660.35 Labeling.

In addition to the items required by § 809.10 of this chapter and other applicable labeling provisions of this chapter, the following information shall be included in the labeling:

(a)(1) A logo or company name may be placed on the final container label, however, the logo or company name shall be located along the bottom or end of the label, oustide of the main panel.

(2) If washing the cells is required by the manufacturer, the container label shall include appropriate instructions; if the cells should not be washed before use, e.g., if washing will adversely affect the product, the package insert shall explain.

(b) The container label of Group O cells shall state:

''FOR USE IN DETECTION OF UNEXPECTED ANTIBODIES'' or ''FOR USE IN IDENTIFICATION OF UNEXPECTED ANTIBODIES'' or ''NOT FOR USE IN DETECTION OR IDENTIFICATION OF UNEXPECTED ANTIBODIES''.

(c) Except as provided in this section, the container and package labels shall state the percentage of red blood cells in the suspension either as a discrete figure with a variance of more than ±1 percentage unit or as a range the extremes of which differ by no more than 2 percentage units. If the stated red blood cell concentration is less than 2 percent, the variance shall be no more than ±0.5 percentage unit.

(d) The words ''pooled cells'' shall appear on the container and package labels of products prepared from pooled cells. The package label or package insert shall state that pooled cells are not recommended for pretransfusion tests, done in lieu of a major crossmatch, to detect unexpected antibodies in patients' samples.

(e) The package insert of a pooled product intended for detection of unexpected antibodies shall identify the number of donors contributing to the

pool. Products designed exclusively for ABO Serum Grouping and umbilical cord cells need not identify the number of donors in the pool.

(f) When the product is a multicontainer product, e.g., a cell panel, the container label and package label shall be assigned the same identifying lot number, and shall also bear a number or symbol to distinguish one container from another. Such number or symbol shall also appear on the antigenic constitution matrix.

(g) The package label or package insert shall state the blood group antigens that have been tested for and found present or absent on the cells of each donor, or refer to such information in an accompanying antigenic constitution matrix. Cells for ABO Serum Grouping are exempt from this requirement. The package insert or antigen constitution matrix shall list each of the antigens tested with only one source of antibody.

(h) The package label or package insert shall bear the cautionary statement: ''The reactivity of the product may decrease during the dating period.''

(i) The package insert of a product intended for the detection or identification of unexpected antibodies shall note that the rate at which antigen reactivity (e.g., agglutinability) is lost is partially dependent upon individual donor characteristics that are neither controlled nor predicted by the manufacturer.

(j) The package insert shall provide adequate directions for use.

(k) The package insert shall bear the statement:

''CAUTION: ALL BLOOD PRODUCTS SHOULD BE TREATED AS POTENTIALLY INFECTIOUS. SOURCE MATERIAL FROM WHICH THIS PRODUCT WAS DERIVED WAS FOUND NEGATIVE WHEN TESTED IN ACCORDANCE WITH CURRENT FDA REQUIRED TESTS. NO KNOWN TEST METHODS CAN OFFER ASSURANCE THAT PRODUCTS DERIVED FROM HUMAN BLOOD WILL NOT TRANSMIT INFECTIOUS AGENTS.''

(l) The package insert or the antigenic constitution matrix for each lot of product shall specify the date of manufacture or the length of the dating period.

(m) Manufacturers shall identify with a permanent donor code in the product labeling each donor of peripheral blood used for detection or identification of unexpected antibodies.

(Approved by the Office of Management and Budget under control number 0910–0073)

§ 660.36 Samples and protocols.

(a) The following shall be submitted to the Office of Biological Product Review Sample Custodian (ATTN: HFB–215), Bldg. 29A, Rm. 1C02, Food and Drug Administration, 8800 Rockville Pike, Bethesda, MD 20892, within 30 days after each routine establishment inspection by FDA.

(1) From a lot of final product, samples from a cell panel intended for identification of unexpected antibodies. The sample shall be packaged as for distribution and shall have at least 14 days remaining in the dating period when shipped to the Center for Biologics Evaluation and Research.

(2) A protocol which shall include the following:

(i) Complete test records of at least two donors of the samples submitted, including original and confirmation phenotyping records.

(ii) Bleeding records or receipt records which indicate collection date, volume, and HBsAg test results.

(iii) Manufacturing records which document all steps involved in the preparation of the product.

(iv) Test results which verify that the final product meets specifications.

(v) Identity test results.

(b) A copy of the antigenic constitution matrix specifying the antigens present or absent shall be submitted to the Director, Center for Biologics Evaluation and Research, at the time of initial distribution of each lot of Reagent Red Blood Cells for detection or identification of unexpected antibodies. Products designed exclusively to identify Anti-A, Anti-A_1, and Anti-B, as well as products composed entirely of umbilical cord cells, are excluded from this requirement.

(c) Except for umbilical cord samples, whenever a new donor is used, a sample of red blood cells from each new donor used in a cell panel intended for

the identification of unexpected antibodies shall be submitted by the manufacturer to the Director, Center for Biologics Evaluation and Research. The sample should contain a minimum volume of 0.5 milliliter of red blood cells.

(Approved by the Office of Management and Budget under control number 0910–0073)

[52 FR 37450, Oct. 7, 1987, as amended at 55 FR 11013 and 11015, Mar. 26, 1990]

Subpart E—Hepatitis B Surface Antigen

SOURCE: 44 FR 36382, June 22, 1979, unless otherwise noted.

§ 660.40 Hepatitis B Surface Antigen.

(a) *Proper name and definition.* The proper name of this product shall be Hepatitis B Surface Antigen (HBsAg), which shall consist of a serum or tissue preparation containing one or more subtypes of the Hepatitis B Surface Antigen.

(b) *Source.* The source of the product shall be blood, plasma, serum, or tissue, obtained aseptically from nonhuman primates that have met the applicable requirements of § 600.11 of this chapter, or from human donors whose blood is positive for the Hepatitis B Surface Antigen.

§ 660.41 Processing.

(a) *Method.* The processing method shall be one that has been shown to yield consistently a specific and potent final product, free of properties which would adversely affect the test results when the product is tested by the methods recommended by the manufacturer in the package insert. The product and all ancillary reagents and materials supplied in the package with the product shall be manufactured in a manner that will reduce the risk of transmitting type B viral hepatitis.

(b) *Ancillary reagents and materials.* All ancillary reagents and materials supplied in the package with the product shall meet generally accepted standards of purity and quality and shall be effectively segregated and otherwise manufactured in a manner that will reduce the risk of contaminating the product and other biological products. Ancillary reagents and materials accompanying the product, which are used in the performance of the test as described by the manufacturer's recommended test procedures, shall have been shown not to affect adversely the product within the prescribed dating period.

(c) *Final container.* A final container shall be sufficiently transparent to permit visual inspection of the contents for presence of particulate matter and increased turbidity. The effectiveness of the contents of a final container shall be maintained throughout its dating period.

(d) *Date of manufacture.* The date of manufacture of Hepatitis B Surface Antigen that has been iodinated with radioactive iodine (^{125}I) shall be the day of labeling the antibody with the radionuclide.

[44 FR 36382, June 22, 1979, as amended at 49 FR 1685, Jan. 13, 1984]

§ 660.42 Reference panel.

A Reference Hepatitis B Antiserum Panel shall be obtained from the Center for Biologics Evaluation and Research, 8800 Rockville Pike, Bethesda, MD 20892, and shall be used for determining the potency and specificity of Hepatitis B Surface Antigen.

[44 FR 36382, June 22, 1979, as amended at 49 FR 23834, June 8, 1984; 51 FR 15611, Apr. 25, 1986; 55 FR 11013, Mar. 26, 1990]

§ 660.43 Potency test.

To be satisfactory for release, each filling of Hepatitis B Surface Antigen shall be tested against the Reference Hepatitis B Antiserum Panel and shall be sufficiently potent to be able to detect the antibody in the appropriate sera of the reference panel by all test methods recommended by the manufacturer in the package insert.

§ 660.44 Specificity.

Each filling of the product shall be specific for Hepatitis B Surface Antigen as determined by specificity tests found acceptable to the Director, Center for Biologics Evaluation and Research.

[44 FR 36382, June 22, 1979, as amended at 49 FR 23834, June 8, 1984; 55 FR 11013, Mar. 26, 1990]

§ 660.45 Labeling.

In addition to the requirements of §§ 610.60, 610.61, and 809.10 of this chapter, the labeling shall bear the following:

(a) The ''d and y'' antigen subtype and the source of the product to follow immediately the proper name on both the final container label and the package label. If the product is intended to identify antibodies to the ''r and w'' antigen subtype, the antigen subtype designation shall include the ''r and w'' antigen subtype.

(b) The name of the test method(s) recommended for use of the product on the package label and on the final container label, when capable of bearing a full label (see § 610.60(a) of this chapter).

(c) A warning on the package label and on the final container label stating that the product is capable of transmitting hepatitis and should be handled accordingly.

(d) The package shall include a package insert providing (1) detailed instructions for use, (2) an adequate description of all recommended test methods, and (3) warnings as to possible hazards, including hepatitis transmitted in handling the product and any ancillary reagents and materials accompanying the product.

§ 660.46 Samples; protocols; official release.

(a) *Samples.* (1) For the purposes of this section, a sample of product not iodinated with ^{125}I means a sample from each filling of each lot packaged as for distribution, including all ancillary reagents and materials; and a sample of product iodinated with ^{125}I or unlyophilized HBsAg-coated red blood cells means a sample from each lot of diagnostic test kits in a finished package, including all ancillary reagents and materials.

(2) Unless the Director, Center for Biologics Evaluation and Research, determines that the reliability and consistency of the finished product can be assured with a smaller quantity of sample or no sample and specifically reduces or eliminates the required quantity of sample, each manufacturer shall submit the following samples to the Director, Center for Biologics Evaluation and Research (HFB–1), 8800 Rockville Pike, Bethesda, MD 20892, within 5 working days after the manufacturer has satisfactorily completed all tests on the samples:

(i) One sample until written notification of official release is no longer required under paragraph (c)(2) of this section.

(ii) One sample of product at periodic intervals of 90 days, beginning after written notification of official release is no longer required under paragraph (c)(2) of this section. The sample submitted at the 90-day interval shall be from the first lot or filling, as applicable, released by the manufacturer, under the requirements of § 610.1 of this chapter, after the end of the previous 90-day interval. The sample shall be identified as ''surveillance sample'' and shall include the date of manufacture.

(iii) Samples may at any time be required to be submitted to the Director, Center for Biologics Evaluation and Research, if the Director finds that continued evaluation is necessary to ensure the potency, quality, and reliability of the product.

(b) *Protocols.* For each sample submitted as required in paragraph (a)(1) of this section, the manufacturer shall send a protocol that consists of a summary of the history of manufacture of the product, including all results of each test for which test results are requested by the Director, Center for Biologics Evaluation and Research. The protocols submitted with the samples at periodic intervals as provided in paragraph (a)(2)(ii) of this section shall be identified by the manufacturer as ''surveillance test results.''

(c) *Official release.* (1) The manufacturer shall not distribute the product until written notification of official release is received from the Director, Center for Biologics Evaluation and Research, except as provided in paragraph (c)(2) of this section. Official release is required for at least five consecutive lots or fillings, as applicable, manufactured after licensure of the product.

(2) After written notification of official release is received from the Director, Center for Biologics Evaluation and Research, for at least five consecutive lots or fillings manufactured after

licensure of the products, and after the manufacturer receives from the Director, Center for Biologics Evaluation and Research, written notification that official release is no longer required, subsequent lots or fillings may be released by the manufacturer under the requirements of §610.1 of this chapter.

(3) The manufacturer shall not distribute lots or fillings, as applicable, of products that require sample submission under paragraph (a)(2)(iii) of this section until written notification of official release or notification that official release is no longer required is received from the Director, Center for Biologics Evaluation and Research.

[48 FR 20407, May 6, 1983, as amended at 49 FR 23834, June 8, 1984; 51 FR 15611, Apr. 25, 1986; 55 FR 11013 and 11014, Mar. 26, 1990]

Subpart F—Anti-Human Globulin

§ 660.50 Anti-Human Globulin.

(a) *Proper name and definition.* The proper name of this product shall be Anti-Human Globulin which shall consist of one or more antiglobulin antibodies identified in §660.55(d) and be prepared by a method demonstrated to yield consistently a sterile product.

(b) *Source.* The source of this product shall be either serum from animals immunized with one or more human serum globulins or protein-rich fluids derived from stable immunoglobulin-secreting cell lines maintained either in tissue cultures or in secondary hosts.

[50 FR 5579, Feb. 11, 1985]

§ 660.51 Processing.

(a) *Processing method.* (1) The processing method shall be one that has been shown to yield consistently a specific, potent final product, free of properties that would adversely affect the product for its intended use throughout its dating period.

(2) Anti-IgG, –C3d (polyspecific) reagents and anti-IgG products may be colored green.

(3) Only that material which has been fully processed, thoroughly mixed in a single vessel, and sterile filtered shall constitute a lot. Each lot shall be identified by a lot number.

(4) A lot may be subdivided into clean, sterile vessels. Each subdivision shall constitute a sublot which shall be identified by the lot number to which has been added a distinctive prefix or suffix. If lots are to be subdivided, the manufacturer shall include this information in the license application and on the protocol. The manufacturer shall describe the test specifications to verify that each sublot is identical to other sublots of the lot.

(b) *Final containers and dropper assemblies.* (1) Final containers and dropper assemblies shall be clean.

(2) Final containers and dropper pipettes shall be colorless and sufficiently transparent to permit observation of the contents for presence of particulate matter or increased turbidity.

(c) *Date of manufacture.* The date of manufacture shall be the date the manufacturer begins the last entire group of potency tests.

(Approved by the Office of Management and Budget under control number 0910–0208)

[50 FR 5579, Feb. 11, 1985, as amended at 50 FR 16474, Apr. 26, 1985]

§ 660.52 Reference preparations.

Reference Anti-Human Globulin preparations shall be obtained from the Center for Biologics Evaluation and Research (HFB–221), Food and Drug Administration, 8800 Rockville Pike, Bethesda, MD 20892, and shall be used as described in the accompanying package insert for determining the potency of Anti-Human Globulin.

(Approved by the Office of Management and Budget under control number 0910–0208)

[50 FR 5579, Feb. 11, 1985, as amended at 50 FR 16474, Apr. 26, 1985; 51 FR 15611, Apr. 25, 1986; 55 FR 11015, Mar. 26, 1990]

§ 660.53 Controls for serological procedures.

Red blood cells sensitized with complement shall be tested with appropriate positive and negative control antisera. All tests shall be performed in accordance with serological testing procedures approved by the Director, Center for Biologics Evaluation and

Research (HFB–1), Food and Drug Administration, 8800 Rockville Pike, Bethesda, MD 20892.

(Approved by the Office of Management and Budget under control number 0910–0208)

[50 FR 5579, Feb. 11, 1985, as amended at 50 FR 16474, Apr. 26, 1985; 51 FR 15611, Apr. 25, 1986; 55 FR 11014, Mar. 26, 1990]

§ 660.54 Potency tests, specificity tests, tests for heterospecific antibodies, and additional tests for nonspecific properties.

The following tests shall be performed using test procedures approved by the Director, Center for Biologics Evaluation and Research (HFB–1), Food and Drug Administration, 8800 Rockville Pike, Bethesda, MD 20892:

(a) Potency tests for determining anti-IgG and anti-complement activity.

(b) Specificity tests, tests for heterospecific antibodies, and additional tests for nonspecific properties.

(Approved by the Office of Management and Budget under control number 0910–0208)

[50 FR 5579, Feb. 11, 1985, as amended at 50 FR 16474, Apr. 26, 1985; 51 FR 15611, Apr. 25, 1986; 55 FR 11014, Mar. 26, 1990]

§ 660.55 Labeling.

In addition to the applicable labeling requirements of §§ 610.62 through 610.65 and § 809.10 of this chapter, and in lieu of the requirements in §§ 610.60 and 610.61 of this chapter, the following requirements shall be met:

(a) *Final container label*—(1) *Color coding.* The main panel of the final container label of all Anti-IgG, –C3d (polyspecific) reagents shall be white or colorless and printing shall be solid dark contrasting lettering. The main panel of the final container label of all other Anti-Human Globulin reagents shall be black with solid white lettering. A logo or company name may be placed on the final container label, however, the logo or company name shall be located along the bottom or end of the label, outside of the main panel.

(2) *Required information.* The proper name ''Anti-Human Globulin'' need not appear on the final container label provided the final container is distributed in a package and the package label bears the proper name. The final container label shall bear the following information:

(i) Name of the antibody or antibodies present as set forth in paragraph (d) of this section. Anti-Human Globulin may contain one or more antibodies to either immunoglobulins or complement components but the name of each significant antibody must appear on the final container label (e.g., anti-C3b, –C3d, –C4d). The final container labels of polyspecific Anti-Human Globulin are not required to identify antibody specificities other than anti-IgG and anti-C3d but the reactivity of the Anti-Human Globulin shall be accurately described in the package insert.

(ii) Name, address, and license number of the manufacturer.

(iii) Lot number, including any sublot designations.

(iv) Expiration date.

(v) Source of the product.

(vi) Recommended storage temperature in degrees Celsius.

(vii) Volume of product.

(viii) Appropriate cautionary statement if the Anti-Human Globulin is not polyspecific. For example, ''DOES NOT CONTAIN ANTIBODIES TO IMMUNOGLOBULINS'' or ''DOES NOT CONTAIN ANTIBODIES TO COMPLEMENT COMPONENTS.''

(ix) If the final container is not enclosed in a package, all items required for a package label shall appear on the container label.

(3) *Lettering size.* The type size for the designation of the specific antibody on the label of a final container shall be not less than 12 point, unless otherwise approved by the Director, Center for Biologics Evaluation and Research (HFB–1). The prefix anti- and other parts of the name such as polyspecific may appear in smaller type.

(4) *Visual inspection.* When the label has been affixed to the final container, a sufficient area of the container shall remain uncovered for its full length or for no less than 5 millimeters of the lower circumference to permit inspection of the contents.

(b) *Package label.* The following items shall appear either on the package label or on the final container label if see-through packaging is used:

(1) Proper name of the product, and the name of the antibody or antibodies as listed in paragraph (d) of this section.

(2) Name, address (including zip code), and license number of the manufacturer.

(3) Lot number, including any sublot designations.

(4) Expiration date.

(5) Preservative(s) used and its concentration.

(6) Number of containers, if more than one.

(7) Recommended storage temperature in degrees Celsius.

(8) Source of the product.

(9) Reference to enclosed package insert.

(10) The statement: ''For In Vitro Diagnostic Use.''

(11) The statement: ''Meets FDA Potency Requirements.''

(12) A statement of an observable indication of an alteration of the product, e.g., turbidity, color change, precipitate, that may indicate possible deterioration of the product.

(13) Appropriate cautions.

(c) *Package insert.* Each final container of Anti-Human Globulin shall be accompanied by a package insert meeting the requirements of §809.10 of this chapter. If two or more final containers requiring identical package inserts are placed in a single package, only one package insert per package is required.

(d) *Names of antibodies.*

Antibody designation on container label	Definition
(1) Anti-IgG, -C3d; Polyspecific.	Contains anti-IgG and anti-C3d (may contain other anticomplement and anti-immunoglobulin antibodies).
(2) Anti-IgG	Contains anti-IgG with no anti-complement activity (not necessarily gamma chain specific).
(3) Anti-IgG; heavy chains.	Contains only antibodies reactive against human gamma chains.
(4) Anti-C3b	Contains only C3b antibodies with no anti-immunoglobulin activity. **Note:** The antibody produced in response to immunization is usually directed against the antigenic determinant which is located in the C3c subunit; some persons have called this antibody ''anti-C3c.'' In product labeling, this antibody should be designated anti-C3b.
(5) Anti-C3d	Contains only C3d antibodies with no anti-immunoglobulin activity.
(6) Anti-C4b	Contains only C4b antibodies with no anti-immunoglobulin activity.
(7) Anti-C4d	Contains only C4d antibodies with no anti-immunoglobulin activity.

Anti-Human Globulin preparations may contain one or more of the antibody specificities listed in this paragraph as described in paragraph (a)(2)(i) of this section.

(Approved by the Office of Management and Budget under control number 0910–0208)

[50 FR 5579, Feb. 11, 1985; 50 FR 9800, Mar. 12, 1985, as amended at 50 FR 16474, Apr. 26, 1985; 55 FR 11014, Mar. 26, 1990]

PART 680—ADDITIONAL STANDARDS FOR MISCELLANEOUS PRODUCTS

Sec.

AUTHORITY: 21 U.S.C. 321, 351, 352, 353, 355, 360, 371; 42 U.S.C. 216, 262, 263, 263a, 264.

SOURCE: 38 FR 32100, Nov. 20, 1973, unless otherwise noted.

CROSS REFERENCES: For U.S. Customs Service regulations relating to viruses, serums, and toxins, see 19 CFR 12.21–12.23. For U.S. Postal Service regulations relating to the admissibility to the United States mails see parts 124 and 125 of the Domestic Mail Manual, that is incorporated by reference in 39 CFR part 111.

§ 680.1 Allergenic Products.

(a) *Definition.* Allergenic Products are products that are administered to man for the diagnosis, prevention or treatment of allergies.

(b) *Source materials*—(1) *Criteria for source material.* Only specifically identified allergenic source materials that contain no more than a total of 1.0 percent of detectable foreign materials shall be used in the manufacture of Allergenic Products, except that this requirement shall not apply to molds and animals described under paragraphs (b)(2) and (3) of this section, respectively. Source materials such as pelts, feathers, hairs, and danders shall be collected in a manner that will minimize contamination of the source material.

(2) *Molds.* (i) Molds (excluding rusts and smuts) used as source material in

the manufacture of Allergenic Products shall meet the requirements of § 610.18 of this chapter and § 680.2 (a) and (b).

(ii) Mold cultures shall be free of contaminating materials (including microorganisms) prior to harvest, and care shall be taken to minimize contamination during harvest and subsequent processing.

(iii) Mold manufacturers shall maintain written standard operating procedures, developed by a qualified individual, that will ensure the identity of the seed culture, prescribe adequate processing of the mold, and specify the acceptable limits and kinds of contamination. These limits shall be based on results of appropriate tests performed by the manufacturer on at least three consecutive lots of a mold that is a representative species of mold subject to the standard operating procedures. The tests shall be performed at each manufacturing step during and subsequent to harvest, as specified in the standard operating procedures. Before use of the mold as a source material for Allergenic Products, in accordance with 21 CFR 601.2, the standard operating procedures and test data from the three representative lots described above shall be submitted to and approved by the Director, Center for Biologics Evaluation and Research (HFB–1).

(3) *Mammals and birds*—(i) *Care of animals.* Animals intended as a source material for Allergenic Products shall be maintained by competent personnel in facilities or designated areas that will ensure adequate care. Competent veterinary care shall be provided as needed.

(ii) *Health of animals.* Only animals in good health and free from detectable skin diseases shall be used as a source material for Allergenic Products. The determination of good health prior to collection of the source material shall be made by a licensed veterinarian or a competent individual under the supervision and instruction of a licensed veterinarian provided that the licensed veterinarian certifies in writing that the individual is capable of determining the good health of the animals.

(iii) *Immunization against tetanus.* Animals of the equine genus intended as a source material for Allergenic Products shall be treated to maintain immunity to tetanus.

(iv) *Reporting of certain diseases.* In cases of actual or suspected infection with foot and mouth disease, glanders, tetanus, anthrax, gas gangrene, equine infectious anemia, equine encephalomyelitis, or any of the pock diseases among animals intended for use or used as source material in the manufacture of allergenic Products, the manufacturer shall immediately notify the Director, Center for Biologics Evaluation and Research (HFB–1).

(v) *Dead animals.* Dead animals may be used as source material in the manufacture of Allergenic Products: *Provided,* That (*a*) the carcasses shall be frozen or kept cold until the allergen can be collected, or shall be stored under other acceptable conditions so that the postmortal decomposition processes do not adversely affect the allergen, and (*b*) when alive, the animal met the applicable requirements prescribed in paragraphs (b)(3) (i), (ii), and (iii) of this section.

(vi) *Mammals and birds inspected by the U.S. Department of Agriculture.* Mammals and birds, subject to inspection by the U.S. Department of Agriculture at the time of slaughter and found suitable as food, may be used as a source material, and the requirements of paragraph (b)(3) (i) through (iv) of this section do not apply in such a case. Notwithstanding U.S. Department of Agriculture inspection, the carcasses of such inspected animals shall be frozen or kept cold until the allergen is collected, or shall be stored under other acceptable conditions so that the postmortal decomposition processes do not adversely affect the allergen.

(c) *Listing of source materials and suppliers.* Each licensed manufacturer shall initially list with the Director, Center for Biologics Evaluation and Research (HFB–1), the name and address of each of the manufacturer's source material suppliers. The listing shall identify each source material obtained from each source material supplier. The licensed manufacturers shall update the listing annually to include

new source material suppliers or to delete those no longer supplying source materials.

(d) *Exemptions.* (1) Exemptions or modifications from the requirements under paragraph (b) of this section shall be made only upon written approval by the Director, Center for Biologics Evaluation and Research (HFB–1).

(2) Nonlicensed source material suppliers are exempt from drug registration.

(Approved by the Office of Management and Budget under control number 0910–0124 for paragraph (b)(2)(iii) and control number 0910–0161 for paragraph (c))

[38 FR 32100, Nov. 20, 1973, as amended at 49 FR 25432, June 21, 1984; 49 FR 31395, Aug. 7, 1984; 55 FR 11014, Mar. 26, 1990]

§680.2 Manufacture of Allergenic Products.

(a) *Extraneous allergenic substances.* All manufacturing steps shall be performed so as to insure that the product will contain only the allergenic and other substances intended to be included in the final product.

(b) *Cultures derived from microorganisms.* Culture media into which organisms are inoculated for the manufacture of Allergenic Products shall contain no allergenic substances other than those necessary as a growth requirement. Neither horse protein nor any allergenic derivative of horse protein shall be used in culture media.

(c) *Liquid products for oral administration.* Liquid products intended for oral administration that are filled in multiple dose final containers shall contain a preservative in a concentration adequate to inhibit microbial growth.

(d) *Residual pyridine.* Products for which pyridine is used in manufacturing shall have no more residual pyridine in the final product than 25 micrograms per milliliter.

(e) [Reserved]

(f) *Records.* A record of the history of the manufacture or propagation of each lot of source material intended for manufacture of final Allergenic Products shall be available at the establishment of the manufacturer of the source material, as required by §211.188 (OMB control number 0910–0139) of this chapter. A summary of the history of the manufacture or propagation of the source material shall be available at the establishment of the manufacturer of the final product.

[38 FR 32100, Nov. 20, 1973, as amended at 49 FR 25433, June 21, 1984]

§680.3 Tests.

(a) *Identity.* When a specific identity test meeting the provisions of §610.14 of this chapter cannot be performed, the manufacture of each lot shall be separated from the manufacture of other products in a manner that will preclude adulteration, and records made in the course of manufacture shall be in sufficient detail to verify the identity of the product.

(b) *Safety.* A safety test shall be performed on the contents of a final container of each lot of each product as prescribed in §610.11 of this chapter, except for the following:

(1) For lots consisting of no more than 20 final containers or 20 sets of individual dilutions, or where the final container contains no more than one intended human dose, the safety test need not be performed on the contents of a final container provided the safety test is performed on each lot of stock concentrate and on each lot of diluent contained in the final product. Only stock concentrates and diluents which have passed the general safety test shall be kept in the work areas used for the manufacture of Allergenic Products. A stock concentrate is an extract derived from a single allergenic source and used in the manufacture of more than one lot of product, and from which final dilutions or mixtures, are prepared directly.

(2) For powders for scratch tests, a sample shall be suspended in a suitable diluent and injected into each animal, and the sample size shall be the single human dose recommended.

(c) *Sterility.* A sterility test shall be performed on each lot of each Allergenic Product as prescribed in §610.12 of this chapter, with the following exceptions:

(1) When bulk material is not prepared, the sterility test prescribed for bulk material shall be performed on

each container of each stock concentrate at the time a stock concentrate is prepared, and the test sample shall be no less than 1 ml. from each stock concentrate container.

(2) For lots consisting of no more than 5 final containers, the final container test shall be performed in accordance with § 610.12(g)(6) of this chapter using the sample therein prescribed or using a sample of no less than 0.25 ml. of product from each final container, divided in approximately equal proportions for testing in Fluid Thioglycollate and Soybean-Casein Digest Media. The test sample in the later alternative method may be an overfill in the final container.

(3) For products prepared in sets of individual dilution series, a test sample of 0.25 ml. shall be taken from a final container of each dilution, which samples may be pooled and one half of the pooled material used for the test with Fluid Thioglycollate Medium and one half used for the test with Soybean-Casein Digest Medium.

(4) Tablets and capsules need not be tested for sterility provided aseptic techniques are employed in their manufacture.

(d) [Reserved]

(e) *Potency.* The potency of each lot of each Allergenic Product shall be determined as prescribed in § 610.10 of this chapter. Except as provided in this section, the potency test methods shall measure the allergenic activity of the product. Until manufacturers are notified by the Director, Center for Biologics Evaluation and Research, of the existence of a potency test that measures the allergenic activity of an allergenic product, manufacturers may continue to use unstandardized potency designations.

(f) *Records.* The records related to the testing requirements of this section shall be prepared and maintained as required by §§ 211.165, 211.167, 211.188, and 211.194 of this chapter.

(Information collection requirements in this section were approved by the Office of Management and Budget under control number 0910–0139)

[38 FR 32100, Nov. 20, 1973, as amended at 39 FR 19777, June 6, 1974; 41 FR 4015, Jan. 28, 1976; 52 FR 37607, Oct. 8, 1987; 55 FR 11013, Mar. 26, 1990]